Anal. Calcd. for $C_{44}H_{66}O_{22}N_6$: C, 53.60; H, 3.57; N, 7.10. Found: C, 53.6, 53.7; H, 3.6, 3.6; N, 7.4, 7.5.

Triglycerol from the Oxidation of O-α,α'-Diallylglycerol with Potassium Permanganate.—To a mixture of O-α,α'-diallylglycerol (86.0 g., 0.5 mole) and water (600 cc.) cooled to 3° was added, with stirring, a solution of potassium permanganate (160 g., 1.01 mole) in water (3200 cc.) over a period of five hours. The temperature was kept at 3–5°. At the end of the addition the mixture was allowed to stand at room temperature for one and one-half hours, during which time the reaction temperature rose to 10°. The mixture was subsequently warmed to 25° and allowed to stand one hour longer after which the manganese dioxide was removed and the filtrate and washings were neutralized with concentrated hydrochloric acid (21.8 cc.). The aqueous solution was evaporated *in vacuo* to dryness and the residue was extracted with methanol. Removal of the methanol yielded a viscous sirup which was dissolved in ethyl alcohol. Benzene was added and the solvents were distilled in an attempt to remove the last trace of water azeotropically. A solution of the resulting sirup in absolute methanol was dried over anhydrous sodium sulfate. Filtration and removal of the methanol from the filtrate yielded 126.1 g. of a viscous water-white sirup (theoretical yield 121.1 g.). Undoubtedly impurities such as higher oxidation products were present as evidenced by the yield of isopropylidene derivatives.

The crude triglycerol (90 g.) was acetonated according to the procedure described above (750 cc. of acetone, 7.5 g. of anhydrous hydrogen chloride, 100 g. of anhydrous sodium sulfate). There resulted 75 g. (65.6% over-all yield based on diallylglycerol) of crude material which on distillation yielded 54 g. (approximately 47.2%) of a mixture of isopropylidene- and diisopropylidenetriglycerols. The mixture of isopropylidene derivatives was separated by fractional distillation into one fraction which was chiefly diisopropylidenetriglycerol (b. p. 162° (2 mm.)) and a higher boiling fraction (distillation range 190–220° (4–9 mm.)) which was primarily isopropylidenetriglycerol.

The first fraction (29 g.) was hydrolyzed to triglycerol as described above, yielding a viscous liquid (21.7 g., 100%) which on distillation gave 16.2 g. of sirupy triglycerol having a $n^{25}D$ of 1.4931. This value was higher than that shown by the sirupy triglycerol from the performic acid hydroxylation, probably because the proportion of isomers present was different, as shown by the following crystallization studies. The isolation of the crystalline isomer was effected as detailed above. Approximately 50% of the triglycerol prepared by this procedure was isolated as crystalline material as compared to 25–33% isolated from the sirupy triglycerol mixture resulting from the performic acid hydroxylation. The crystalline triglycerol prepared by the two methods had identical melting points (98–99°) which were not depressed on admixture. In this preparation, as in the previous one, the sirupy residue isolated from the mother liquor ($n^{25}D$ 1.4800) could not be induced to crystallize, nor could it be converted to a crystalline derivative.

Anal. Calcd. for $C_9H_{20}O_7$: C, 44.99; H, 8.39. Found: C, 45.1, 44.9; H, 8.1, 8.2.

Summary

1. Triglycerol has been synthesized by the hydroxylation of O-α,α'-diallylglycerol by the action of performic acid and by the action of permanganate.

2. Crystalline triglycerol of melting point 98–99° has been isolated and identified.

3. Triglycerol was isolated from the reaction mixtures by conversion to its isopropylidene derivatives and subsequent distillation.

MINNEAPOLIS, MINNESOTA RECEIVED MAY 16, 1949

[CONTRIBUTION FROM THE LABORATORY OF ORGANIC CHEMISTRY OF THE UNIVERSITY OF WISCONSIN]

Steroid Analogs Lacking Ring C. I. The Synthesis of 6-Cyclohexyl-Δ^{1-9}-octalone-2 by the Robinson–Mannich Base Method

BY CLIFFORD H. SHUNK[1,2] AND A. L. WILDS

For some time we have been interested in the synthesis of certain analogs of the steroid hormones progesterone, desoxycorticosterone and testosterone lacking ring C. The first stage in this work, started in 1941 and interrupted during the war, has been to apply the Robinson–Mannich base synthesis[3] of cyclic α,β-unsaturated ketones to 4-cyclohexylcyclohexanone (I), obtaining 6-cyclohexyl-Δ^{1-9}-octalone-2 (VIII). Since we were interested in extending the reactions to less readily available derivatives of the ketone I, we have looked in some detail into several methods of applying this synthesis.

The best yields in the Robinson–Mannich base synthesis have been obtained with ketones having the adjacent methylene group activated, and accordingly we first investigated the carbomethoxy derivative III, as in our previous work in the chrysene series.[4] This was prepared from the ketone I *via* the glyoxylate II, although in poor yield (*ca.* 12%) primarily because of the decarbonylation step. The next reaction with the methiodide of 1-diethylaminobutanone-3 proceeded in good yield to the diketo ester IV, and the latter could be cyclized to 6-cyclohexyl-Δ^{1-9} octalone-2 (VIII) in fair yield (48%) with aqueous alkali or acid. With sodium methoxide the carbomethoxy group was retained giving IX.

Because of the poor over-all yields by this method, and particularly in the decarbonylation of the glyoxylate II, the latter derivative itself was used for condensation with the Mannich base methiodide. However, cyclization of the resulting product gave the octalone VIII in less than 20% yield.

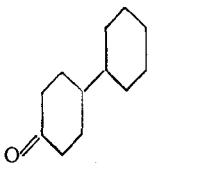
It seemed attractive to try the hydroxymethyl-

(1) Wisconsin Alumni Research Foundation Research Assistant, 1941–1942; National Research Council Predoctoral Fellow 1946–1948.

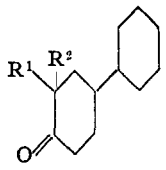
(2) Present address, Merck and Co., Inc., Rahway, N. J.

(3) *Cf.* du Feu, McQuillin and Robinson, *J. Chem. Soc.*, 53 (1937), and subsequent papers.

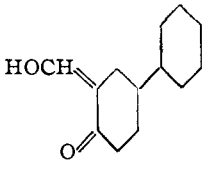
(4) Wilds and Shunk, THIS JOURNAL, **65**, 469 (1943).



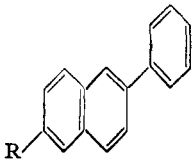
I



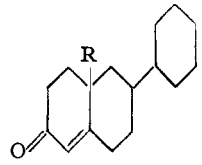
II, R^1 = H; R^2 = —COCOOCH$_3$
III, R^1 = H; R^2 = —COOCH$_3$
IV, R^1 = $CH_3COCH_2CH_2$—; R^2 = —COOC$_4$H
V, R^1 = $CH_3COCH_2CH_2$—; R^2 = —CHO
VI, R^1 = $CH_3COCH_2CH_2$—; R^2 = H



VII



X, R = H
XI, R = —OH



VIII, R = H
IX, R = —COOCH$_3$

ene derivative VII, since this group can be introduced into ketones in excellent yield[5] and after alkylation is very easily eliminated.[6] Apparently hydroxymethylene ketones have not been employed previously in the Mannich base condensation. As high as 87% of the derivative VII could be obtained from the ketone I employing an excess of ethyl formate and sodium methoxide. There was no indication of any bis-hydroxymethylene derivative being formed[7]; the ultraviolet absorption spectrum showed a single maximum at 281 mμ.[8]

Reaction of the hydroxymethylene ketone VII with 1-diethylaminobutanone-3 methiodide resulted in introduction of the γ-ketobutyl group in excellent yield; the product consisted of V, in which the formyl group was retained, and VI in which this had been eliminated, the ratio of the two varying with the reaction conditions. Each was cyclized smoothly with acid, or preferably with dilute methanolic alkali at room temperature for two to three hours. The over-all yield of 6-cyclohexyl-Δ^{1-9}-octalone-2 from 4-cyclohexylcyclohexanone was about 60–65%. By following the ultraviolet absorption spectrum it was possible to determine rather easily the relative effectiveness of various cyclizing reagents and the optimum conditions for maximum yield.[9]

(5) *Cf.* Johnson, Anderson and Shelberg, THIS JOURNAL, **66**, 220 (1944); Johnson and Shelberg, *ibid.*, **67**, 1745 (1945).

(6) *Cf.* Wilds and Djerassi, *ibid.*, **68**, 1715 (1946).

(7) This is in agreement with the findings of Prelog and Metzler with cyclopentanone, *Helv. Chim. Acta.*, **30**, 878 (1947).

(8) This illustrates the fact that a β-OH group results in a greater shift of the maximum for α,β-unsaturated ketones than an alkyl group [*cf.* Woodward, THIS JOURNAL, **63**, 1123 (1941); **64**, 76 (1942)], amounting to about 50 mμ compared to 35 mμ for an α-OH [Fieser, Fieser and Rajagopalan, *J. Org. Chem.*, **13**, 800 (1948)].

(9) Although the octalone VIII can exist in two racemic isomers which would be expected to be in equilibrium under the conditions of cyclization (due to ready shift of the double bond), only one isomer could be obtained, with no direct evidence for the presence of the other form.

Evidence confirming the structure of the octalone was obtained by dehydrogenation to 2-phenylnaphthalene (X) and 6-phenyl-2-naphthol (XI).

Experimental[10]

4-Cyclohexylcyclohexanone (I).—4-Hydroxybiphenyl was hydrogenated[11] in absolute ethanol at 140° and 2000 p. s. i. using W-6 Raney nickel catalyst[12]; the mixture of isomeric 4-cyclohexylcyclohexanols was obtained in 96% yield, m. p. in the range 80–105°. Forty grams of this mixture was dissolved in 500 ml. of glacial acetic acid and stirred at 15–18° while a solution of 30 g. of chromium trioxide in 40 ml. of water and 100 ml. of acetic acid was added slowly over a period of one hour. After an additional hour at the same temperature 50 ml. of methanol was added, the mixture allowed to stand one-half hour and then the solvent was removed under reduced pressure. The gummy residue was dissolved in dilute hydrochloric acid and ether, and the ether layer washed thoroughly with acid, dilute sodium hydroxide and water. From the ether extract was obtained 34.6 g. (87%) of the ketone, b. p. 98–100° (0.1 mm.), m. p. 30–31° (reported,[13] 31°). The semicarbazone melted at 215–216° (reported[13] 216°).

From the alkaline extract was obtained an oily acid which crystallized from ether-petroleum ether, 0.97 g. (2%), m. p. 92–93°. Further recrystallization from carbon tetrachloride did not change the m. p. of the product, evidently β-cyclohexyladipic acid. The yield of this acid was increased using higher temperatures during the oxidation.

Anal. Calcd. for $C_{12}H_{20}O_4$: C, 63.1; H, 8.8. Found: C, 62.9; H, 8.8.

2-Hydroxymethylene-4-cyclohexylcyclohexanone (VII).—The following modification of the general procedure of Johnson, Anderson and Shelberg,[5] employing three moles of sodium methoxide and five moles of ethyl formate per mole of ketone, gave the best yields. The sodium methoxide prepared from 4.8 g. of sodium and 50 ml. of dry methanol was freed of excess solvent, finally heating at 160° under reduced pressure for one-half hour, cooled under nitrogen, 25 ml. of dry benzene added and distilled again to dryness. The solid was broken up, suspended in 50 ml. of dry, thiophene-free benzene and stirred while 30 ml. of dry ethyl formate was added. After one-half hour at room temperature the mixture was cooled in an ice-bath, a solution of 13.0 g. of 4-cyclohexylcyclohexanone in 100 ml. of benzene was added and the ice-bath removed. To the yellow gelatinous mixture was then added 150 ml. of benzene and stirring was continued overnight at room temperature. Ice-cold water was added and the benzene layer extracted with two portions of cold 2% sodium hydroxide. After washing the combined alkaline layers with ether and acidifying, the resulting oil was extracted thoroughly with chloroform, washed and dried over sodium sulfate. The light orange oil remaining after the chloroform was removed under reduced pressure was distilled (capillary tube attached to a source of nitrogen) giving 13.1 g. (87%) of nearly colorless hydroxymethylene derivative, b. p. 114–116° (0.1 mm.).[14] Redistillation gave material, b. p. 113° (0.1 mm.), which had an absorption maximum at 281 mμ (E = 8,690).[15,16] The compound, which gave a purple color with alcoholic ferric chloride, was unstable and decomposed after a few days even when sealed in an ampule.

(10) All melting points are corrected.

(11) *Cf.* Musser and Adkins, THIS JOURNAL, **60**, 664 (1938).

(12) Adkins and Billica, *ibid.*, **70**, 695 (1948).

(13) v. Braun, *Ann.*, **472**, 60 (1929).

(14) When equivalent amounts of sodium methoxide, ethyl formate and ketone were used the yield was only 66%.

(15) Absorption spectra were determined in 95% ethanol using a Beckman quartz spectrophotometer; E = molecular extinction coefficient.

(16) There was no indication of a peak at longer wave lengths corresponding to the bis-hydroxymethylene derivative.

Anal. Calcd. for $C_{13}H_{20}O_2$: C, 75.0; H, 9.7. Found: C, 74.6; H, 9.5.

The **copper enolate**, prepared in 88% yield by shaking an ether solution of the hydroxymethylene ketone with a saturated solution of cupric acetate, was recrystallized from benzene to give clusters of fine green needles that decomposed at 228–229°.

Anal. Calcd. for $C_{26}H_{38}O_4Cu$: C, 65.3; H, 8.0; Cu, 13.3. Found: C, 65.7; H, 8.1; Cu,[17] 13.4.

The **aniline derivative** was prepared by adding 90 mg. of aniline to 100 mg. of hydroxymethylene ketone in 1 ml. of methanol. After one hour at room temperature 99 mg. (73%) of solid was obtained, m. p. 114–118°. Recrystallization from methanol gave light yellow prisms, m. p. 115–117°.

Anal. Calcd. for $C_{19}H_{25}ON$: C, 80.5; H, 8.9. Found: C, 80.5; H, 8.9.

2-Formyl-2-(γ-ketobutyl)-4-cyclohexylcyclohexanone (V).—To a solution of 1.45 g. of sodium in 50 ml. of dry methanol was added 13.07 g. of the hydroxymethylene ketone VII dissolved in 50 ml. of methanol. The solution was cooled in an ice-bath and then treated with 50 ml. of methanol containing the methiodide prepared from 18 g. of 1-diethylaminobutanone-3.[18] The solution was allowed to come to room temperature as the ice melted and after standing overnight 12.94 g. (67%) of white needles was collected, washing with methanol. This material, m. p. 121–123° (gas evol.), was found to contain one molecule of methanol even after drying at 65° (0.1 mm.) overnight; the melting point was not changed by further recrystallization.[19]

Anal. Calcd. for $C_{17}H_{26}O_3 \cdot CH_3OH$: C, 69.7; H, 9.7. Found: C, 69.7; H, 9.7.

After the above solid was filtered from the reaction mixture, the filtrate was poured into ice-cold dilute sodium hydroxide, extracted with benzene–ether, washed with cold dilute acid, water and dried over sodium sulfate. Distillation gave 4.84 g. of an oil, b. p. 140–155° (0.1 mm.), which from analysis appeared to consist of approximately two parts of VI, from which the formyl group had been eliminated (21%) to one part of V retaining the formyl group (9%), corresponding to a total yield of 97%.

Anal. Calcd. for $C_{16}H_{26}O_2$ (formyl group eliminated): C, 76.7; H, 10.5. Calcd. for $C_{17}H_{26}O_3$: C, 73.3; H, 9.4. Found: C, 75.6, 75.4; H, 10.2, 10.2.

The ratio of solid to oily product varied in different experiments. In one run using two parts methanol to one of benzene for the solvent, there resulted 7% of the solid, m. p. 112–114°, and 92% of oil, evaporatively distilling below 170° (0.1 mm.), corresponding in analysis to the solvent-free formyl derivative V.

Found: C, 73.2, 73.1; H, 9.5, 9.5.

6-Cyclohexyl-Δ^{1-9}-octalone-2 (VIII) from 2-Formyl-2-(γ-ketobutyl)-4-cyclohexanone (V). (a) Acid Cyclization.—Preliminary cyclization experiments were carried out by dissolving 100 mg. of the formyl derivative (V, containing one molecule of methanol) in 25 ml. of acetic acid, adding 5 ml. of concentrated hydrochloric acid and allowing to stand at room temperature. At intervals samples were withdrawn, evaporated under reduced pressure and the extent of cyclization determined from the ultraviolet absorption in ethanol at 239 mμ, with the following results: one hour, 45%; two hours, 59%; four hours, 70%; six and one-half hours, 80%; thirty-seven hours, 82%. At reflux, the cyclization appeared to be complete in less than one-half hour (one-half hour, 82%; one and one-half hour, 82%; two and one-half hours, 78%).

On the basis of these preliminary results, a solution of 2.0 g. of the solid formyl derivative V in 190 ml. of acetic acid was treated with 40 ml. of concentrated hydrochloric acid and allowed to stand at room temperature for sixteen hours. The solvent was then removed under reduced pressure followed by several portions of alcohol, leaving 1.55 g. of a red oil, E_{239} = 12,900 (corresponding to a 79% yield). The oil was partially crystallized from 10 ml. of petroleum ether (40–60°) by cooling with Dry Ice, giving 0.29 g., m. p. 37–39°. Evaporative distillation of the filtrate at 145° (0.1 mm.) gave 1.13 g. of colorless distillate which yielded another 0.25 g. of the solid, m. p. 34–37°. Chromatographic adsorption of the remaining oil on alumina gave in the ether-petroleum ether (1:4 and 2:3) eluates an additional 0.16 g. of solid, m. p. 36–39° and 0.097 g. of oily ketone (E_{239} = 10,700). The total yield of solid ketone was 47%. Further recrystallization yielded colorless prisms, m. p. 41.5–42.5°, with an absorption maximum at 239 mμ, E = 17,000.[15]

Anal. Calcd. for $C_{16}H_{24}O$: C, 82.7; H, 10.4. Found: C, 82.8; H, 10.5.

The **semicarbazone**, prepared in 95% yield by the alcohol–pyridine procedure, was recrystallized from ethanol, m. p. 223–224°. The same semicarbazone was obtained whether the solid ketone or the oily filtrates were used.

Anal. Calcd. for $C_{17}H_{27}ON_3$: C, 70.6; H, 9.4. Found: C, 70.7; H, 9.2.

The **2,4-dinitrophenylhydrazone**, prepared in methanol containing a drop of hydrochloric acid, crystallized from ethyl acetate–ethanol as a red solid, m. p. 202–203°.

Anal. Calcd. for $C_{22}H_{28}O_4N_4$: C, 64.1; H, 6.8. Found: C, 63.8; H, 6.7.

In another run as above, acid cyclization of 2 g. of the solid formyl derivative gave 1.55 g. of oil (E_{239} = 12,800, indicating a 78% yield) which was converted directly to the semicarbazone. Digestion of the crude derivative (1.57 g., m. p. 210–215°) gave with hot alcohol 1.34 g., m. p. 223–224°, corresponding to a 72% yield.

(b) **Alkaline Cyclization.**—Preliminary experiments with 200 mg. of the solid formyl derivative V in 50 ml. of methanol and 4 ml. of water containing 2 g. of potassium hydroxide (nitrogen atmosphere), indicated alkaline cyclization to be rapid at room temperature (fifteen minutes, 55%; one hour, 84%; two and one-half hours, 90%; three and one-half hours, 88%; five hours, 81%).

On this basis, to 500 ml. of methanol through which nitrogen was bubbling was added 20 g. of potassium hydroxide in 40 ml. of water followed by 5.29 g. of the solid formyl derivative V (containing methanol). After two and one-quarter hours at room temperature the slightly yellow solution was poured into 1500 ml. of saturated sodium chloride solution and extracted with four portions of ether, washing the latter with water and drying over sodium sulfate. Removal of the solvent left 3.83 g. of light yellow oil, E_{239} = 14,400, which corresponded to an 82% yield. By crystallization from petroleum ether using Dry Ice 2.68 g. (68%) of solid, m. p. 35–37°, was obtained. Evaporative distillation of the filtrate at 165° (0.1 mm.) yielded 0.96 g. of oil. Conversion of the latter to the semicarbazone, m. p. 215–217°, indicated it contained 0.55 g. of the ketone, bringing the total yield to 82%.

A similar alkaline cyclization of 3.87 g. of the oil (found above to correspond to two parts of the formyl derivative V to one part of the derivative VI with the formyl group eliminated) gave 3.17 g. of oily ketone (E_{239} = 12,000 or 65% yield) from which 2.03 g. (59%) of the crystalline ketone, m. p. 33–36°, could be obtained.

Dehydrogenation of 6-Cyclohexyl-Δ^{1-9}-octalone-2.—A solution of 1 g. of the octalone derivative VIII in 6 ml. of *p*-cymene and 0.2 g. of 30% palladium on carbon[20] was

(17) Determined by weighing residual cupric oxide in boat after carbon–hydrogen analysis.

(18) The methiodide was prepared as described previously (ref. 4) adding the methyl iodide in small portions with cooling (vigorous reaction) and allowing each to react before adding more.

(19) When 200 mg. of the solid was heated at 150°, 17 mg. of distillate was obtained and shown to be methanol by conversion to methyl 3,5-dinitrobenzoate, m. p. 106–107°, undepressed when mixed with a known sample. That the methanol might not be merely solvent of crystallization was indicated by repeated failure to induce the solvent-free compound (see below) to crystallize from methanol.

(20) Linstead and Thomas, *J. Chem. Soc.*, 1130 (1940).

heated to reflux under nitrogen. After nineteen hours an additional 0.1 g. of catalyst was added and heating continued for a total of forty-three hours. Since only 182 ml. of hydrogen had been evolved, the mixture was filtered after diluting with benzene, evaporated and the residue heated with 0.1 g. of fresh catalyst at 320° for one hour (260 ml. of hydrogen evolved). The product was dissolved in ether and extracted with several portions of 10% potassium hydroxide. The residue from the ether was evaporatively distilled at 160° (0.1 mm.) and crystallized from methanol to give 0.04 g. (5%) of **2-phenylnaphthalene** (X), m. p. 96–98°. The m. p. was raised to 101–102° by further recrystallization (reported,[21] 101.5°). From the alkaline extracts after evaporative distillation at 150–165° (0.1 mm.) and crystallization from benzene was obtained 0.27 g. (28%) of **6-phenyl-2-naphthol** (XI), m. p. 176–177°. Recrystallization from benzene raised the m. p. to 177–178° (reported,[22] 175–176°).

Anal. Calcd. for $C_{16}H_{12}O$: C, 87.2; H, 5.5. Found: C, 87.1; H, 5.3.

The **methyl ether of 6-phenyl-2-naphthol**, prepared with alkali and methyl sulfate and recrystallized from methanol, melted at 148–149° (reported,[22] 148°).

2-Methoxalyl-4-cyclohexylcyclohexanone (II).—To the methanol-free sodium methoxide prepared from 0.86 g. of sodium was added 30 ml. of dry benzene and 4.4 g. of dimethyl oxalate. The mixture was refluxed for ten minutes under nitrogen with stirring, then cooled in an ice-bath and 6.72 g. of 4-cyclohexylcyclohexanone (I) added in 20 ml. of benzene. After standing at room temperature for one and one-half hours, the light orange solution was extracted with three portions of ice-cold 2% sodium hydroxide, the latter acidified and extracted with ether. The ether extract was washed with sodium bicarbonate solution, water, dried over sodium sulfate and evaporated, leaving 6.0 g. (60%) of a light yellow oil which gave a purple color with alcoholic ferric chloride solution.

One gram of this oil in 10 ml. of ether gave 0.66 g. (59%) of the green **copper enolate derivative** (dec. at 220–222°). Recrystallization from benzene raised the decomposition point to 224–225°.

Anal. Calcd. for $C_{30}H_{42}O_8Cu$: C, 60.6; H, 7.1; Cu, 10.7. Found: C, 60.5; H, 7.1; Cu,[17] 10.6.

From the bicarbonate extract of the crude glyoxylate was obtained 1.3 g. of a viscous red oil from which was crystallized 0.28 g. of a solid, m. p. 110–114°, using carbon tetrachloride–petroleum ether. Triturating this solid with hot benzene and filtering gave 0.03 g. of material m. p. 213–215°.[23] From the filtrate was obtained 0.19 g. of a different compound, m. p. 115–116°. Recrystallization of the lower melting compound from benzene did not change its melting point. The analysis of compound, which gave a red color with alcoholic ferric chloride, indicated it to be the free glyoxylic acid derivative (corresponding to II).

Anal. Calcd. for $C_{14}H_{20}O_4$: C, 66.6; H, 8.0. Found: C, 66.3; H, 8.1.

2-Carbomethoxy-4-cyclohexylcyclohexanone (III).—A 11.4-g. sample of the 2-methoxalyl derivative II, not purified by extraction with bicarbonate, was heated at 180° with 10 g. of powdered soft glass for thirty minutes. The red oil was dissolved in ether and extracted with cold dilute sodium hydroxide. From the ether after washing and drying was obtained 6.3 g. of a red oil from which was obtained 4.85 g. (48%) of colorless distillate boiling below 140° (0.5 mm.). Redistillation gave 1.2 g., b. p. 84–90° (0.1 mm.), which proved to be largely 4-cyclohexylcyclohexanone, 1.1 g., b. p. 90–115° (0.1 mm.), and 2.3 g. (23%) of the carbomethoxy derivative, b. p. 115–118° (0.1 mm.), or b. p. 134° (0.6 mm.).

Anal. Calcd. for $C_{14}H_{22}O_3$: C, 70.6; H, 9.3. Found: C, 70.9; H, 9.2.

When methoxalyl derivative which had been washed with bicarbonate was employed, 37% of crude material distilling below 160° (0.5 mm.) was obtained.

The **pyrazolone derivative, 5-cyclohexyl-4,5,6,7-tetrahydro-3-indazolone** was prepared by heating 1.0 g. of the crude undistilled oil with 0.8 g. of hydrazine sulfate, 1 ml. of pyridine and 10 ml. of methanol for four hours. Treatment with water and ether yielded 0.44 g. of white solid, m. p. 234–238°. Recrystallization of the derivative from ethyl acetate–acetic acid raised the m. p. to 239–243°.

Anal. Calcd. for $C_{13}H_{20}ON_2$: C, 70.9; H, 9.2. Found: C, 70.9; H, 9.2.

2-Carbomethoxy-2-(γ-ketobutyl)-4-cyclohexylcyclohexanone (IV).—To 0.23 g. of sodium dissolved in 10 ml. of methanol was added 2.4 g. of the 2-carbomethoxy derivative III in 10 ml. of benzene. After refluxing for ten minutes the solution was cooled in ice and a solution of the methiodide from 2.90 g. of 1-diethylaminobutanone-3 in 10 ml. of methanol was added. After standing overnight at room temperature and refluxing for one hour, the cooled mixture was diluted with water and extracted with ether, washing the latter with dilute acid and drying over sodium sulfate. The oil (2.90 g.) remaining after removal of the solvent solidified after standing for three months. Recrystallization from ether–petroleum ether (40–60°) gave colorless platelets, m. p. 74–75°.

Anal. Calcd. for $C_{18}H_{28}O_4$: C, 70.1; H, 9.2. Found: C, 70.3; H, 8.9.

10-Carbomethoxy-6-cyclohexyl-Δ^{1-9}-octalone-2 (IX).—To a solution of 250 mg. of sodium in 25 ml. of methanol was added 149 mg. of the above oily 2-carbomethoxy diketone IV, and the mixture was refluxed under nitrogen for two hours, cooled, diluted with water and extracted with benzene-ether. From the washed and dried extract was obtained a yellow oil which was evaporatively distilled at 165° (0.05 mm.) giving 86 mg. of oil which yielded 24 mg. (17%) of colorless needles, m. p. 110–111°. Recrystallization from methanol did not raise the m. p.

Anal. Calcd. for $C_{18}H_{26}O_3$: C, 74.4; H, 9.0. Found: C, 74.4; H, 8.9.

The **semicarbazone** was prepared by the alcohol-pyridine procedure and recrystallized from chloroform-methanol, m. p. 204–206°.

Anal. Calcd. for $C_{19}H_{29}O_3N_3$: C, 65.7; H, 8.4. Found: C, 65.3; H, 8.6.

6-Cyclohexyl-Δ^{1-9}-octalone-2 (VIII) **from 2-Carbomethoxy-2-(γ-ketobutyl)-4-cyclohexylcyclohexanone** (IV).—Alkaline cyclization[24] of 250 mg. of the oily carbomethoxy derivative IV was carried out by refluxing and stirring under nitrogen with 25 ml. of 5% aqueous potassium hydroxide for twenty hours. After isolation and evaporative distillation at 165° (0.1 mm.), 110 mg. of distillate was obtained which yielded 113 mg. of crude semicarbazone of the octalone derivative, m. p. 209–211°, mixed m. p. 210–213°. This corresponds to a 48% yield.

Acid cyclization[24] of 270 mg. of the carbomethoxy derivative IV by heating at reflux for twenty hours with 25 ml. of acetic acid and 5 ml. of hydrochloric acid gave 220 mg. of oily octalone after evaporative distillation.

When 2.0 g. of the 2-methoxalyl derivative II was allowed to react with the methiodide of 1-diethylaminobutanone-3 and a 240-mg. portion of the product (1.67 g. of neutral oil) cyclized[24] by refluxing with 25 ml. of methanol containing 2.5 ml. of 45% potassium hydroxide for four hours, 60 mg. of evaporatively distilled, oily octalone derivative VIII was obtained, which yielded 39

(21) Chattaway and Lewis, *J. Chem. Soc.*, **65**, 872 (1894).

(22) Hey and Lawton, *J. Chem. Soc.*, 383 (1940).

(23) Recrystallization of this higher melting compound from acetone–benzene raised the m. p. to 214–215°. The compound gave an orange color with alcoholic ferric chloride; from the analysis it is suggested, tentatively, that it may be 5-phenyl-2-ketosuberic acid, arising from a trace of 4-phenylcyclohexanone in the starting ketone. Calcd. for $C_{14}H_{16}O_5$: C, 63.6; H, 6.1. Found: C, 63.6; H, 6.2.

(24) These undoubtedly are not the best conditions for cyclization.

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.

MADISON 6, WISCONSIN RECEIVED JULY 1, 1949

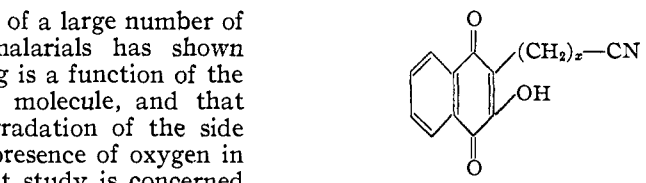
[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF HARVARD UNIVERSITY]

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

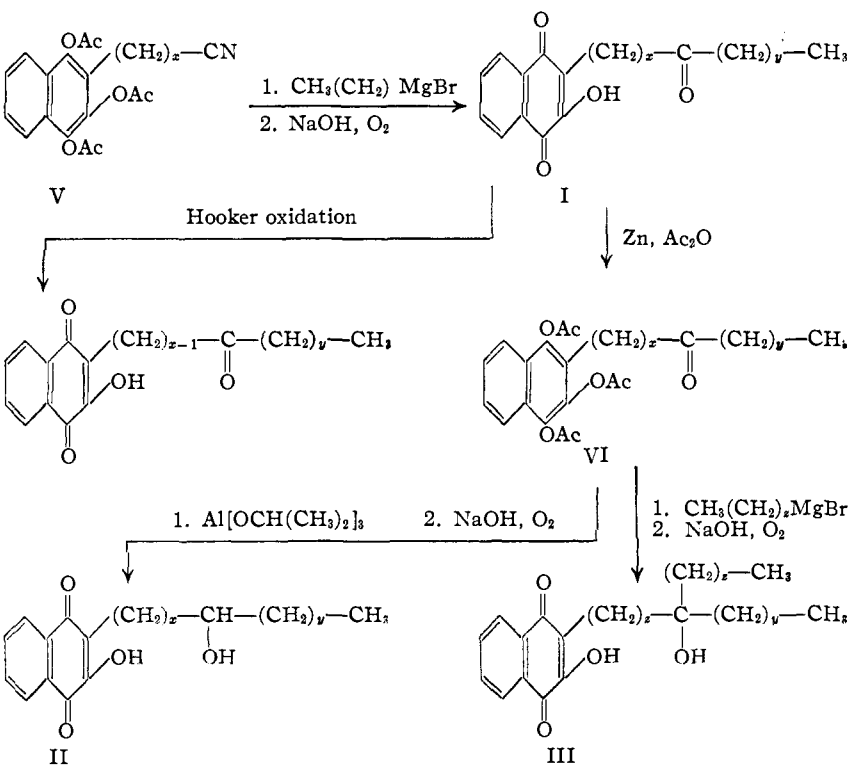
BY DONALD J. CRAM[2]

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,



IV



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

(1) This problem was assigned to the author by Louis F. Fieser.

(2) National Research Predoctoral Fellow, 1946–1947; present address: Department of Chemistry, University of California, Los Angeles 24, California.

(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).