The Oxidation of Dunnione with Alkaline Hydrogen Peroxide*

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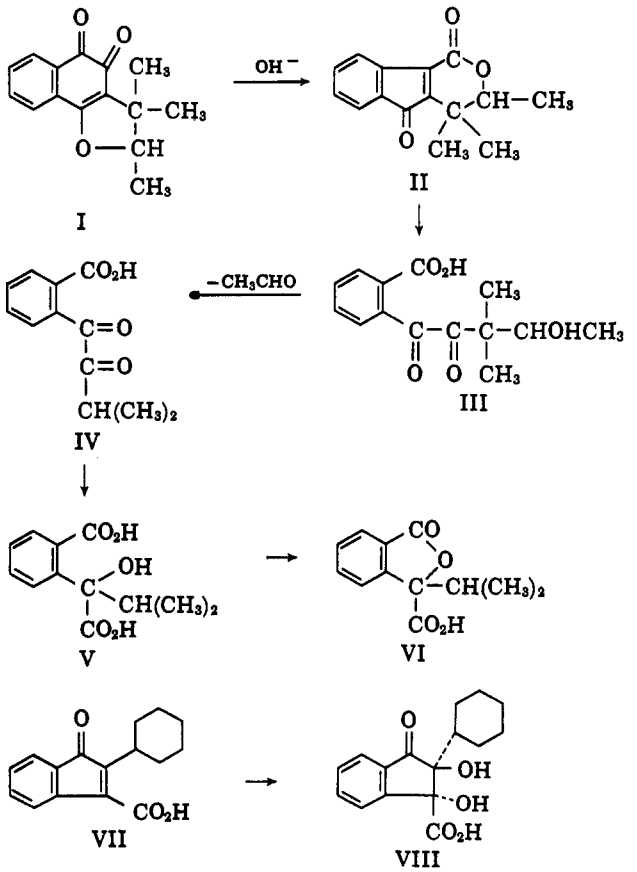
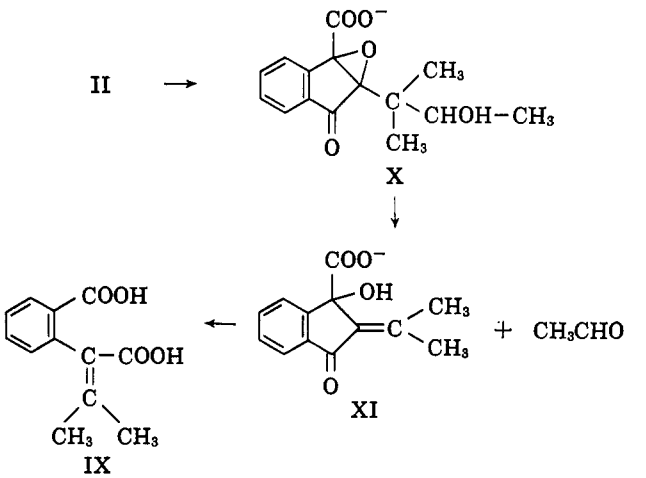
Dunnione, the orange-red pigment of *Streptocarpus dunnii* Mast., has been shown by degradation[1,2] and synthesis[3,4] to be the *o*-naphthoquinone I. Treatment of I with alkali yields allodunnione (II) *via* a rearrangement common to all 2-hydroxy-3-alkyl-1,4-naphthoquinones.[5] The oxidation of dunnione and of allodunnione in alkali with hydrogen peroxide yields[1,2] acetaldehyde, phthalic acid, and a white, crystalline acid, $C_{12}H_{12}O_4$, m.p. 205–206°, formulated as the five-membered lactonic acid VI. This acid was presumed to be formed from allodunnione (II) by oxidation and loss of acetaldehyde from III by a reverse aldol condensation, followed by a benzilic acid rearrangement of IV and ring closure of V to VI. The alkaline hydrogen peroxide oxidation of indenonecarboxylic acids similar to allodunnione yields[6] diols such as VIII from VII, and as Price and Robinson[1,2] had not shown the $C_{12}H_{12}O_4$ oxidation product to be lactonic, we reinvestigated this substance.



Following the published procedure[1] for the oxidation of natural dunnione, we obtained the crystalline acid, the infrared spectrum of which has its carbonyl absorptions between 5.9 and 6.0 μ, thus excluding VI for the structure of this oxidation product. This appeared to be a dicarboxylic acid and comparison with the known[7] α-isopropylidenehomophthalic acid (IX) by mixture melting point and by ultraviolet and infrared spectra established their identity. The structure of IX was confirmed by n.m.r. spectra of the acid and its dimethyl ester.

Presumably the oxidations of allodunnione and VII proceed *via* the epoxides, but while the epoxide of VII is simply hydrolyzed to the diol, the epoxide X more



easily cleaves to acetaldehyde and XI. Such cleavages of derivatives of 1,3-diols are well known.[8] The formation[8d] of merolimonol from limonol appears particularly like the present example.

Paths for the oxidation of XI to IX can be written either by way of 2-isopropyl-1,3-indandione and V or through diverse rearrangements of known type,[9] some involving ring contraction to benzocyclobutenes. The degradation is certainly interesting, but since evidence is lacking, we refrain from further details of possible mechanisms.

Experimental

The oxidation of natural dunnione exactly as described[1] yields a crystalline, optically inactive solid, the melting point of which varies somewhat with the rate of heating from 205 to 215°; λ_{max}^{MeOH} 204 mμ (log ϵ 4.40) and 278 mμ (log ϵ 3.18).

α-Isopropylidenehomophthalic acid[7] made *via* its monomethyl ester, m.p. 141°, has infrared and ultraviolet spectra superimposable on those of the oxidation product. The melting point of a mixture is not depressed.

Proton magnetic resonance spectra for the isopropylidenehomophthalic acid were kindly obtained by Mr. H. E. Miller at Rice University with a Varian A-60 spectrometer (60 Mc.). The acid dissolved with sodium carbonate in deuterium oxide showed only a multiplet from aryl hydrogen atoms centered

* To Professor Louis F. Fieser

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157 c.p.s. below absorption from protons in the water and two equal singlets for the allylic methyl groups at 168 and 193 c.p.s. above the solvent peak. The spectrum of the crude dimethyl ester, prepared with diazomethane in ether and examined in deuteriochloroform, was composed of two singlets for the allylic methyl groups at 95 (presumably *cis* to aryl) and 139 c.p.s. below the tetramethylsilane reference signal, two singlets, also from three protons each, for the carbomethoxyl groups at 217 and 230, a multiplet from three aryl protons at 425–455, and a multiplet from one aryl proton (presumably *ortho* to carbomethoxyl) at 475–487 c.p.s.

6α- and 6β-Hydroperoxy Derivatives of Δ⁴-Cholestenone[1]

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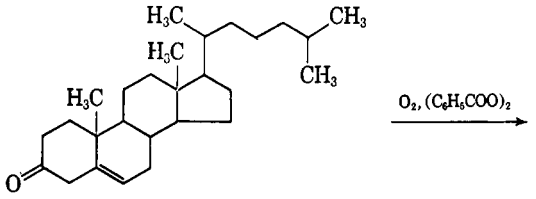
Some years ago, Fieser, Greene, Bischoff, Lopez, and Rapp[4] reported that 6β-hydroperoxy-Δ⁴-cholesten-3-one (**2**) injected in sesame oil in mice produced fibrosarcomas in 13 of 32 mice over a period of 12 months (17 survivors were negative at the time). The hydroperoxide was obtained by combination of Δ⁵-cholesten-3-one with molecular oxygen in hexane solution at 25°, but no preparative details were reported.



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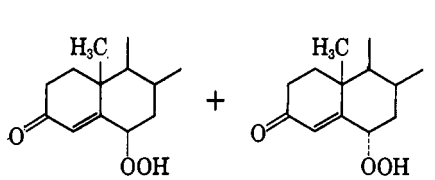

2 **3**

In view of recent interest in the oxidation of steroids[5] and of β,γ-unsaturated ketones,[6] and in the biological properties of the derived hydroperoxides, it may be of value to record a preparative procedure that affords both the 6α- and 6β-hydroperoxides of Δ⁴-cholestenone, separable by crystallization. Dibenzoyl peroxide was found to catalyze the autoxidation and cyclohexane proved to be a particularly favorable solvent. This is the method referred to by Fieser and Fieser[7] for the preparation of these hydroperoxides.

Experimental

Preparation and Separation of Hydroperoxides.—A mixture of 25 g. of Δ⁵-cholesten-3-one[8] and 580 ml. of cyclohexane was prepared at room temperature in a flask equipped with a reflux condenser and a tube for bubbling air through the liquid. While air bubbling was in progress the temperature was raised to 40–50°. After crystals of ketone had all dissolved 500 mg. of dibenzoyl peroxide was added, and air was bubbled through the solution at a temperature not exceeding 50° for 24–36 hr. At this point evaporation of an aliquot and titration by the method described below indicated the presence of 70–80% of hydroperoxide. The cyclohexane solution was cooled while air was still bubbling through it to aid in separation of the precipitate. This was collected by suction filtration, and concentration of the filtrate afforded further solid product. Crystallization of the total solid (22.5 g.) from ether (at room temperature, then at 0°) gave 6.4 g. of waxy flakes of the 6β-hydroperoxide. The filtrate was concentrated and let stand for several days, when two types of crystals were observed: waxy flakes of the β-hydroperoxide and more compact prismatic crystals of the 6α-hydroperoxide. The prisms (2.5 g.) were separated easily by dissolving away the more soluble flakes in ether. Further fractionation of the mother liquor material by the same method afforded a total of 9.8 g. of the 6β-isomer and 3.9 g. of the 6α-isomer; recrystallization from methanol gave 8.4 g. and 3.0 g. of the pure isomers.

Titration of Hydroperoxide.—The following is a modification of a standard method.[9] A flat-bottomed 300-ml. flask with a ground glass joint connected to a bubble trap containing water was charged with 1.5 g. of sodium bicarbonate and 20 ml. of acetic acid, and a weighed sample of hydroperoxide (up to 0.4 mmole) was dissolved in ethanol in a small vial which was placed upright within the reaction flask. Then 5 ml. of 40% potassium iodide solution was added to the outer liquid and the trap was connected. After about 2 min. carbon dioxide evolution had largely ceased and the flask was shaken to empty the vial and mix the contents. After 10–60 min. in the dark at room temperature the mixture was diluted with 30 ml. of distilled water and titrated with 0.01 *N* sodium thiosulfate solution (1 ml. = 2.08 mg. of cholestenone hydroperoxide).

6β-Hydroperoxy-Δ⁴-cholesten-3-one.—Constants found for fully purified material, m.p. 180–181°, $[\alpha]_D$ +27.2° (*c* 1.5, $CHCl_3$), λ^{EtOH} 235 mμ, agree with those previously reported.

6α-Hydroperoxy-Δ⁴-cholesten-3-one.—Repeated crystallization from methanol gave prisms, m.p. 150–151°, $[\alpha]_D$ 33.3° (*c* 1.5, $CHCl_3$), λ^{EtOH} 241 mμ.

Anal. Calcd. for $C_{27}H_{44}O_3$ (416.62): C, 77.83; H, 10.65. Found: C, 77.59; H, 10.80.

The possibility that the 6α-hydroperoxide arises by epimerization of the 6β-isomer during crystallization was tested by crystallizing 3.4 g. of the β-hydroperoxide from ether at different rates over a 3-week period. No prismatic crystals of the α-isomer could be identified.

Proof of Structures.—In a method adapted from a published one,[10] 50-mg. samples of the 6α- and 6β-hydroperoxide were each treated with 2 ml. of approximately 0.1 *N* lead tetraacetate in acetic acid. After 0.5 hr. at room temperature, addition of a solution of 1 g. of sodium chloride in 10 ml. of water caused precipitation of Δ⁴-cholestene-3,6-dione, which was extracted with ether and crystallized from methanol. The samples melted at 123–124° (λ^{EtOH} 251.5 mμ) and 121–122° and gave no depression when mixed with authentic Δ⁴-cholestene-3,6-dione,[11] m.p. 123–124°.

Reduction was accomplished by dissolving a 150-mg. sample of a 6-hydroperoxy-Δ⁴-cholesten-3-one in ethanol and treating with potassium iodide and acetic acid as in the titration procedure. After standing for 10–20 min., excess sodium thiosulfate solution was added together with enough water to precipitate the

(1) Dedicated to Professor Louis F. Fieser on the occasion of his 66th birthday for his distinguished contributions to teaching, research, and writing in organic chemistry.

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(3) This work was carried out under the direction of Professor Louis F. Fieser in 1957–1958 while the author was on sabbatical leave of absence from Stanford University.

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