similarity in behavior is suggestive that the degree of hydration of a protein is essentially the same in solution as in the crystal.

2. The high densities of β-lactoglobulin crystals suspended in sucrose solutions are due to the diffusion of sucrose into the crystal and to a dehydration of the crystal. These effects on the protein crystal indicate that similar effects are present in solutions and that sucrose is not a suitable medium for density determinations of viruses by sedimentation.

3. The calculated "non-solvent" water of the β-lactoglobulin crystals in sucrose solutions varies widely with the sucrose concentration, making a division of the water crystallization of a protein on this basis of doubtful validity.

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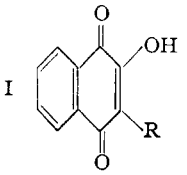
[CONTRIBUTION FROM THE GATES AND CRELLIN LABORATORIES OF CHEMISTRY, CALIFORNIA INSTITUTE OF TECHNOLOGY (NO. 1387), AND THE CHEMICAL LABORATORY OF HARVARD UNIVERSITY]

Hydroxynaphthoquinones. IV. Photochemical β-Oxidation of Side Chains

BY MARTIN G. ETTLINGER[1]

During an investigation[2] of the distribution of hydroxynaphthoquinones between ether and aqueous buffers, it was accidentally observed that a dilute (20 mg./100 cc.) solution of hydrolapachol[3] (I, R = $(CH_2)_2CH(CH_3)_2$) in wet ether decomposed on standing for a week in a flask on a desk top with formation of a more hydrophilic quinone.



The product was isolated by differential buffer extraction and identified as an oxygenated derivative of hydrolapachol, hydroxyisolapachol[4] (I, R = $CH_2COCH(CH_3)_2$). The facile autoxidation of the β-methylene of the side chain to a carbonyl group was new and distinct from hydroxylation of the tertiary γ-carbon of hydrolapachol by metabolic oxidation[5] or chromic anhydride,[6] or quinone ring opening by alkaline permanganate or peroxide.[7]

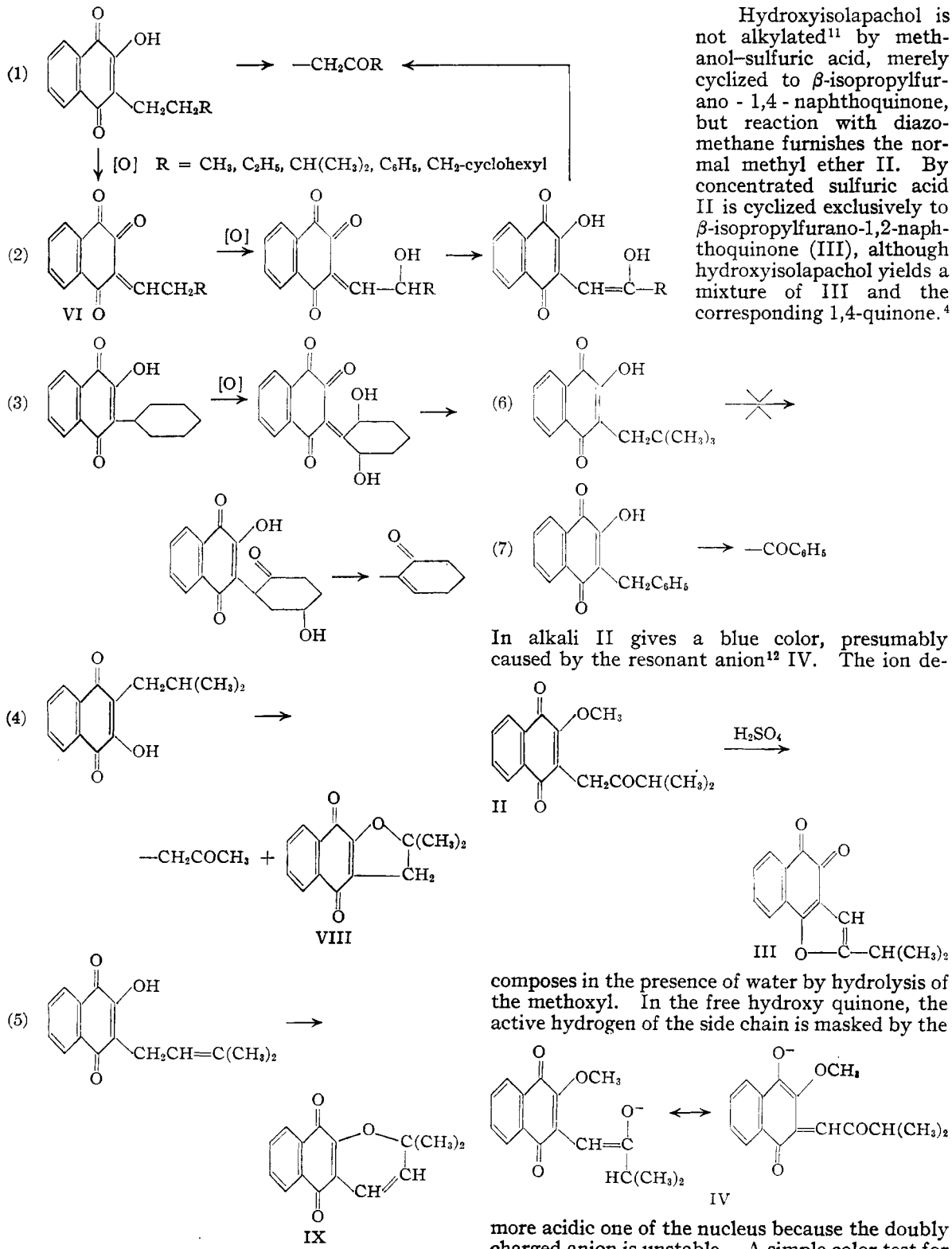
In continued experiments on autoxidation of hydroxynaphthoquinones, the conditions first discovered were generally followed. A quinone was dissolved at the usual concentration 10 mg./100 cc. in ether, which was advantageously saturated with water, and allowed to stand for several weeks in diffuse daylight. In darkness reaction stopped. The rate of oxidation was affected by iron, an inhibitor, and peroxides as well as the intensity of illumination, and was not precisely reproducible. In ordinary experiments with 100 mg. or less of hydrolapachol, the fractions, determined by buffer extraction and colorimetry, of hydroxyisolapachol and unchanged hydrolapachol present were, respectively, after eight to ten days 15–25% and 45–50%, and after sixteen to twenty-four days 15–25% and 10–20%. The missing substance occurred partly as neutral, yellow material, and perhaps as colorless, water soluble acids that escaped detection.

If hydrolapachol in dilute, wet ethereal solution was illuminated directly by the sun or a high pressure mercury arc, it was gradually destroyed with the appearance of bright, light blue fluorescence. If, while a majority of the quinone remained, the solution was darkened and let stand for one to two days, as much as 12% of oxygenated derivative was formed.

The β-oxidation of hydrolapachol was extended to four other quinones[3,8] containing a chain of two methylene groups adjacent to the nucleus (Eq. (1)). All known β-ketonic 2-hydroxy-1,4-naphthoquinones,[4,9] one new example, and no other product were obtained. The colorimetrically measured yield of oxygenated quinone from the unrecovered *n*-propyl compound was 60%, almost half of which was isolated.

Properties of hydroxyisolapachol, a representative oxidation product, were examined in detail. The difference[2] in extraction number pE between hydrolapachol and hydroxyisolapachol is approximately 3, of which 1 unit can be attributed to the increased acidity[10] and the other 2 units to the more hydrophilic character produced by the oxygen in the side chain. Since the ratio of their distribution constants between ether and an alkaline buffer is 1000, hydrolapachol and its ketonic derivative are easily separable. Whereas hydrolapachol in alkaline solution gives a stable red color, hydroxyisolapachol gives an orange[4,10] which fades slowly (half-life of 10 mg./100 cc. solution two weeks) in contact with air. In concentrated sulfuric acid, hydroxyisolapachol and alkyl analogs give a characteristic play of colors from orange

(1) Frank B. Jewett Fellow at the California Institute of Technology, 1946–1947.
(2) Fieser, Ettlinger and Fawaz, THIS JOURNAL, 70, 3228 (1948).
(3) For source see Fieser and Richardson, *ibid.*, 70, 3156 (1948).
(4) Hooker, *J. Chem. Soc.*, 69, 1355 (1896).
(5) Fieser, *et al.*, *J. Pharmacol. Exptl. Therap.*, 94, 85 (1948).
(6) Fieser, THIS JOURNAL, 70, 3237 (1948).
(7) Fieser and Fieser, *ibid.*, 70, 3215 (1948).
(8) Fieser, *et al.*, *ibid.*, 70, 3174 (1948).
(9) Hooker and Steyermark, *ibid.*, 58, 1202 (1936).
(10) Ettlinger, *ibid.*, 72, 3085 (1950).



to deep brown-red,[4] and 2-hydroxy-3-aroylmethyl-1,4-naphthoquinones one from yellow through green to blue.[6]

Hydroxyisolapachol is not alkylated[11] by methanol–sulfuric acid, merely cyclized to β-isopropylfurano - 1,4 - naphthoquinone, but reaction with diazomethane furnishes the normal methyl ether II. By concentrated sulfuric acid II is cyclized exclusively to β-isopropylfurano-1,2-naphthoquinone (III), although hydroxyisolapachol yields a mixture of III and the corresponding 1,4-quinone.[4]

In alkali II gives a blue color, presumably caused by the resonant anion[12] IV. The ion decomposes in the presence of water by hydrolysis of the methoxyl. In the free hydroxy quinone, the active hydrogen of the side chain is masked by the more acidic one of the nucleus because the doubly charged anion is unstable. A simple color test for 2 - hydroxy - 3 - acylmethyl - 1,4 - naphthoquinones

(11) Zaugg, THIS JOURNAL, 71, 1890 (1949).
(12) Karrer, *Helv. Chim. Acta*, 22, 1146 (1939).

consists in treatment with diazomethane followed by alcoholic alkali. A transient blue color is positive; substances such as lapachol (I, R = $CH_2CH{=}C(CH_3)_2$) and 2-hydroxy-3-benzyl-1,4-naphthoquinone (I, R = $CH_2C_6H_5$), containing a carbon–carbon double bond once removed from the quinone ring, give only a slowly developing orange or red. By this criterion the structure of the oxidation product of the γ-cyclohexylpropyl compound was established.

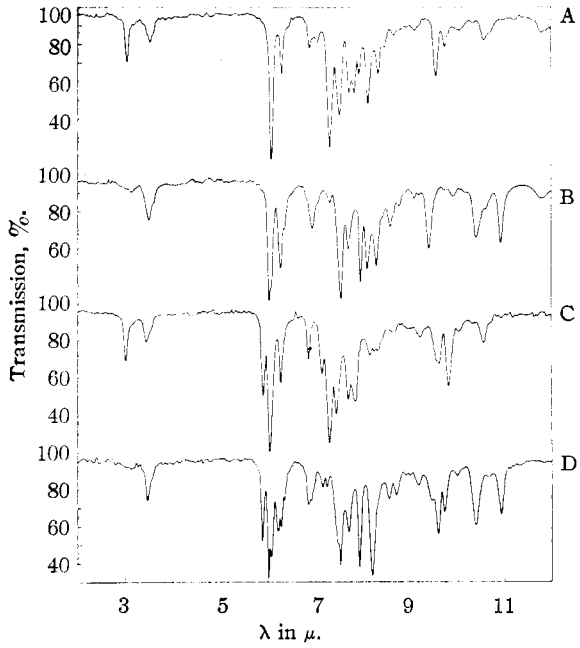
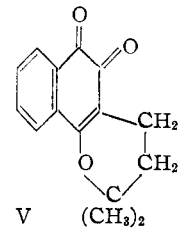


Fig. 1.—Infrared absorption spectra of A, lapachol; B, lapachol methyl ether; C, hydroxyisolapachol; D, hydroxyisolapachol methyl ether. A, B, D for 2% solutions in carbon tetrachloride; C, 2% in chloroform.

Infrared absorption spectra (Fig. 1) served to distinguish an unconjugated carbonyl[13] in a quinone[14] side chain. 2-Hydroxy-1,4-naphthoquinone and its 3-alkyl and phenyl derivatives in dilute solutions in chloroform or carbon tetrachloride have salient maxima at 2.95–3.1 μ, 5.98–6.08 μ, 6.23–6.3 μ, and 7.18–7.35 μ. In their methyl ethers, the 6.03 μ band may be resolved in two, the hydroxyl band near 3 μ is absent, and the 7.25 μ band, which in these substances evidently does not arise from a methyl vibration, vanishes also. The spectra of 2-naphthol and its methyl ether, on the other hand, are similar between 6 and 9 μ. 2-Hydroxy-3-acetonyl-1,4-naphthoquinone, hydroxyisolapachol and its methyl ether have an additional maximum at 5.8–5.88 μ, corresponding to the side chain carbonyl. 1,2-Quinones also may possess a short wave length carbonyl band; β-lapachone (V) absorbs at 5.93, 6.07 and 6.23 μ.

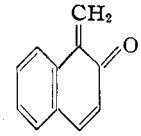
(13) Hartwell, Richards and Thompson, *J. Chem. Soc.*, 1436 (1948); Rasmussen, Tunnicliff and Brattain, THIS JOURNAL, **71**, 1068 (1949).

(14) Flett, *J. Chem. Soc.*, 1441 (1948).



V

The mechanism of autoxidation of the β-methylene of the side chain may be most simply represented by the scheme (2).[15] The first step is an oxidation to the quinone methide VI. A similar molecule, 1-methylene-2-naphthone (VII), is believed to be produced by the decomposition[16] of



VII

dehydrobis-1-methyl-2-naphthol, an analog of the peroxides of hydroxynaphthoquinones.[17] The second step consists in allylic oxidation of the original β-methylene group, probably through a hydroperoxide,[18] and the last in the shift of the double bond away from the carbonyl groups and ketonization[19] of the side chain.

The conditions of β-oxidation were applied to five quinones containing side chains branched or multiply substituted at the α- or β-positions. 2-Hydroxy-3-cyclohexyl-1,4-naphthoquinone[8] (I, R = cyclohexyl) was slowly attacked and gave in 15% yield a *substance*, m. p. 192.5–194.5° (dec.), the composition and infrared spectrum whereof suggested substitution in the side chain of a conjugated carbonyl and double bond. The reaction possibly proceeded according to the outline (3), by dihydroxylation of an intermediate like type VI and dehydration of the resultant β-hydroxy ketone. 2-Hydroxy-3-isobutyl-1,4-naphthoquinone[8] (I, R = $CH_2CH(CH_3)_2$) on standing in diffuse light furnished no crystalline product save a trace of unknown, sparingly soluble, yellow material decomposing at 240°. However, when a wet ethereal solution of the isobutyl compound (25 mg./100 cc.) was exposed in a Pyrex flask to direct sunlight until roughly one-third of the quinone was destroyed (three hours) and then allowed to stand four weeks, there were isolated in 2–3% yield the two known substances 2-hydroxy-3-acetonyl-1,4-napthoquinone[9] (I, R = CH_2COCH_3) and β,β-dimethyldihydrofurano-1,4-naphthoquinone[20] (VIII) (4). The fragmentation of the iso-

(15) Suggested by Dr. R. B. Woodward (1945).

(16) Pummerer and Cherbuliez, *Ber.*, **52**, 1392 (1919); Smith and Horner, THIS JOURNAL, **60**, 676 (1938).

(17) Ettlinger, *ibid.*, **72**, 3472 (1950).

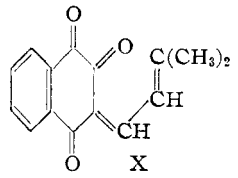
(18) Farmer and Sundralingam, *J. Chem. Soc.*, 121 (1942).

(19) Heilbron, Jones and Spring, *ibid.*, 801 (1937).

(20) Hooker, THIS JOURNAL, **58**, 1168 (1936).

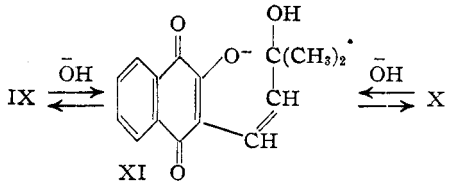
butyl side chain to acetonyl may occur by decomposition[21] of a β-hydroperoxide group.

Lapachol[3] (I, R = $CH_2CH{=}C(CH_3)_2$) in ether was photoöxidized in 25% yield to dehydro-α-lapachone[22] (IX) (5). The process duplicated the extremely slow atmospheric oxidation of crude solid lapachol.[22] The reaction might be considered as an allylic oxidation of the side chain, for example at the γ-position with shift of the double bond to α,β, followed by ring closure. The introduction of allylic hydroxyl at a terminal methyl of lapachol has been accomplished[23] with selenium dioxide. On the other hand, lapachol might be dehydrogenated, in accord with (2), to X. The substance X would be expected to participate in tautomeric equilibrium with dehydrolapachone, either by direct bond rearrangement, which is possible in



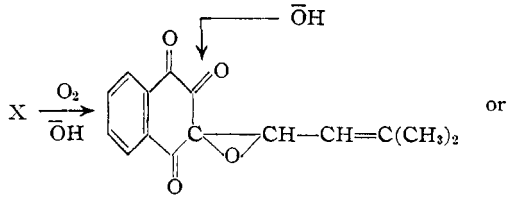
X

any dienone–pyrane system,[24] or, for instance, in base, through the ion XI. Perhaps the singular



XI

degradation of dehydrolapachone to norlapachol (XII) by alkali and air proceeds through X. If it is assumed that the accumulated carbonyls in X sensitize the adjacent double bond to epoxidation by air and base, as quinones and conjugated un-



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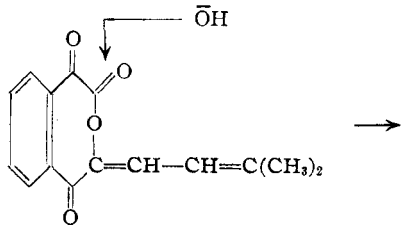
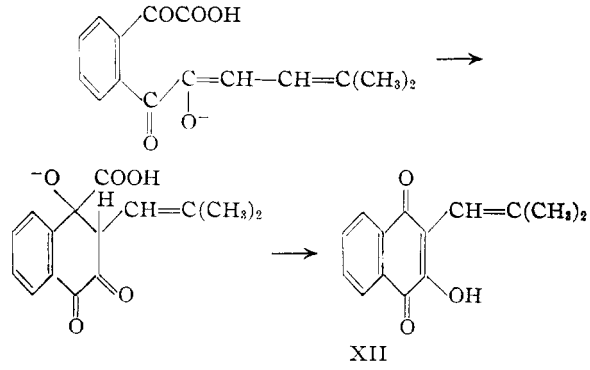
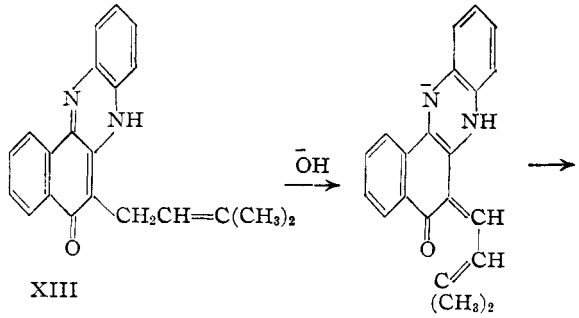


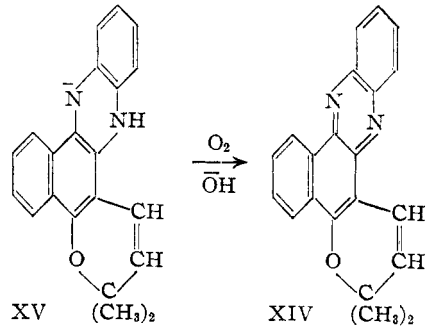


XII

saturated ketones react[25] with alkaline hydrogen peroxide, or else that oxygen is inserted[26] between the double bond and 2-carbonyl, the remaining steps to norlapachol may be formulated by ring opening and a reclosure identical with the last stage of the Hooker oxidation.[7] The oxidation[22] of lapeurhodone (XIII) to dehydrolapazine (XIV) by alkali and air may be represented as a base-catalyzed removal of hydrogen from the α-carbon



XIII

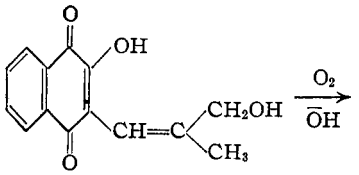


XV XIV

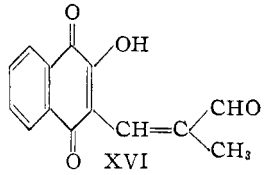
of the side chain,[27] followed by ring closure and oxidation of the ion of the dihydrophenazine. The transformation[28] of XV to XVI, which removes hydrogen from the γ-position, is formally similar.

Two quinones were examined in which the β-position of the side chain was completely substi-

(21) George and Walsh, *Trans. Faraday Soc.*, **42**, 94 (1946).
(22) Hooker, THIS JOURNAL, **58**, 1190 (1936).
(23) Gates, *ibid.*, **70**, 617 (1948).
(24) Hukins nad Le Fevre, *J. Chem. Soc.*, 2088 (1949).
(25) Weitz and Scheffer, *Ber.*, **54**, 2327 (1921); Fieser, Campbell, Fry and Gates, THIS JOURNAL, **61**, 3216 (1939); Bunton and Minkoff, *J. Chem. Soc.*, 665 (1949).
(26) Dakin, *Am. Chem. J.*, **42**, 477 (1909); v. Wacek and v. Bezard, *Ber.*, **74**, 845 (1941); Böeseken and Jacobs, *Rec. trav. chim.*, **55**, 786 (1936).
(27) Fieser and Fieser, THIS JOURNAL, **61**, 596 (1939).
(28) Hooker and Steyermark, *ibid.*, **58**, 1207 (1936).

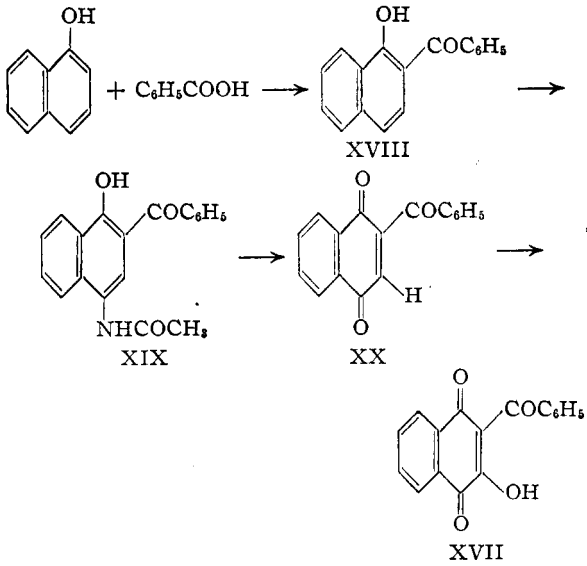


XV



XVI

tuted. 2-Hydroxy-3-neopentyl-1,4-naphthoquinone[8] (I, R = $CH_2C(CH_3)_3$) decomposed to the extent of only 20% during ten weeks (6); no quinone that was more easily extracted formed, and only a trace of neutral, yellow material. 2-Hydroxy-3-benzyl-1,4-naphthoquinone[8] (I, R = $CH_2C_6H_5$) (7) slowly furnished in roughly 10% yield a substance, m. p. 161–162°, which dissolved in alkali and in concentrated sulfuric acid with a yellow color and in alkaline hydrosulfite to a red-brown vat. From its resemblance to 2-hydroxy-3-acetyl-1,4-naphthoquinone[29] and genesis the oxidation product was presumed to be the unknown 2-hydroxy-3-benzoyl-1,4-naphthoquinone (XVII) (7), subsequently described[30] as a result of degradation of 2,3-dibenzoyl-1,4-naphthoquinone. In the present work, the oxidation product was identified by a synthesis modelled on a general preparation of 2-hydroxy-3-acyl-1,4-naphtho-



XVIII XIX XX XVII

quinones.[29] 2-Benzoyl-1-naphthol (XVIII) was nitrated and reduced, and the 4-amino compound acetylated to XIX. The acetylamino derivative was oxidized by nitric acid in acetic acid to 2-benzoyl-1,4-naphthoquinone (XX), which was subjected to a Thiele reaction, followed by hydrolysis of the acetate and oxidation. The resultant authentic XVII and the oxidation product of the benzyl compound were identical.

Acknowledgments.—The author is deeply indebted to Dr. L. F. Fieser, for continued interest and access to the Hooker collection of naphthoquinones, Dr. R. B. Woodward, for helpful discussion, Dr. E. R. Buchman, for the hospitality of his laboratory at the California Institute of Technology, and the trustees of the Frank B. Jewett Fellowships, for financial support.

Experimental

Colorimetry.—Hydroxynaphthoquinones were determined in alkaline solution with a Fisher Electrophotometer (525-mμ filter) or Klett–Summerson Photoelectric Colorimeter (green filter). With either instrument, the molar color density of β-keto quinones was only 65% of that of quinones with alkyl side chains because the former compounds absorb at shorter wave lengths.

Ether Oxidation Procedure.—A hydroxynaphthoquinone was dissolved in ether (10 l./g.), originally commercial anhydrous, that had been shaken with water and separated, and was exposed to diffuse laboratory daylight for several weeks. The progress of degradation was observed by extraction of oxygenated quinone from a sample by an equal volume of buffer (0.2 *N* primary and secondary phosphate) of *p*H perhaps 0.2 unit greater than the *p*E of the starting material,[2] subsequent extraction of unaltered quinone by 0.1 *N* sodium hydroxide, and colorimetry of the aqueous phases. Results, expressed as percentages of starting material oxygenated in the side chain and unattacked, appear in Tables I and II.

TABLE I

AUTOXIDATION OF HYDROLAPACHOL IN ETHER

Concn., mg./100 cc.	Conditions	Time, days	% Buffer-soluble *p*H 8	% Unattacked
10	Wet, dark	41	0	100
10	Wet, light	8	19	49
Solution from preceding row, 8 days in dark			21	54
10	Wet, light	16	23	13
10	Dry, light	25	7	30
10	Wet, sun 1/3 hr.	1	11	38
50	Wet, light	9	5	78
50	Wet, light	17	6	71

For isolation of autoxidation products, an ether solution, at the end of the total period in the table, was concentrated to 50–200 cc., shaken cautiously (evolution of heat) with acidified aqueous ferrous sulfate to destroy peroxides, and extracted with portions of appropriate buffer until the deep orange color of degraded quinone in the aqueous phase was replaced by weak pink from starting material. The ether was shaken with 0.1 *N* sodium hydroxide and evaporated, and the neutral residue examined. The unattacked quinone in the alkali extract was precipitated by acid, weighed and identified. The buffer was washed judiciously with ether and acidified, and the oxygenated quinones were recovered by ether extraction and purified as described individually.

***n*-Propyl.**—The buffer soluble oxidation product from an initial 100 mg. of quinone (solution 1, table II) crystallized from a little ether as 25 mg. (27% of unrecovered starting material) of solid, m. p. 165–171°, which on one crystallization from alcohol afforded 16 mg. of fine, pale yellow needles of 2-hydroxy-3-acetonyl-1,4-naphthoquinone, m. p. 173–175°, undepressed by mixture with an authentic sample.

(29) Cram, THIS JOURNAL, **71**, 3953 (1949).

(30) Dischendorfer, Lercher and Marek, *Monatsh.*, **80**, 333 (1949).

TABLE II

AUTOXIDATION OF HYDROXYNAPHTHOQUINONES IN ETHER

Soln. no.	Side chain	Buffer pH	Special conditions	Time, days	% Buffer-soluble	% Unattacked
1	$(CH_2)_2CH_3$	6.65	Ether peroxide added	33	31	52
				41	37	39
2	$(CH_2)_3CH_3$	7.4		18	25	31
3	$(CH_2)_2C_6H_5$	8.1		17	12	6
4	$(CH_2)_3$-Cyclohexyl	10.2 (glycine-NaOH)		17	36	18
5	Cyclohexyl	8.0	Ether peroxide added	33	(8)	85
				59	(15)	64
				76	(17)	54
				92	(21)	40
6		20 mg./100 cc.; sun 1.5 hr.;	30% of quinone destroyed	7	(13)	43
7	$CH_2CH(CH_3)_2$	7.3	Ether peroxide added	33	(14)	53
				41	(14)	37
8		24 mg./100 cc.; sun 3 hr.;	37% of quinone destroyed	9	(19)	46
				27	(18)	26
9	$CH_2CH{=}C(CH_3)_2$			20	..	33
10	$CH_2C(CH_3)_3$	8.1		28	0	91
				70	0	81
11	$CH_2C_6H_5$	6.6	Ether peroxide added	33		65
				74		28

n-**Butyl**.—The buffer soluble oxidation product from an initial 100 mg. of quinone (solution 2) on three crystallizations from dilute methanol afforded fine, pale yellow needles of 2-hydroxy-3-γ-methylacetonyl-1,4-naphthoquinone, m. p. 162–164.5°, undepressed by mixture with an authentic sample.

Isoamyl.—The buffer soluble oxidation product from an initial 100 mg. of hydrolapachol (row 4, Table I) on two crystallizations from dilute methanol afforded fine, pale yellow needles of hydroxyisolapachol, m. p. 130–132°, which did not depress the melting point of an authentic sample.

Hydroxyisolapachol methyl ether, prepared in 90% yield by the rapid reaction of hydroxyisolapachol and diazomethane in ether and crystallized from ether—petroleum ether, formed yellow blades, m. p. 77–78°.

Anal. Calcd. for $C_{16}H_{16}O_4$: C, 70.57; H, 5.92. Found: C, 70.81; H, 5.89.

In concentrated sulfuric acid, the substance produces an orange coloration, changing quickly to emerald green. Dilution with water of the green solution from 25 mg. of the methyl ether and crystallization of the red precipitate from dilute alcohol furnished 11 mg. (47%) of orange-red needles of β-isopropylfurano-1,2-naphthoquinone, m. p. 91–92.5°.

Hydroxyisolapachol methyl ether, treated in alcoholic solution with 0.1 *N* aqueous sodium hydroxide, gives a blue coloration, which turns rapidly to orange because of hydrolysis to hydroxyisolapachol (isolated and identified). Sodium carbonate hydrolyzes the ether without intermediate color. The test was applied conveniently by treatment of an alcoholic solution of the ether (1 mg./cc.), cooled to 0°, with a few drops of 5% alcoholic potassium hydroxide. The color was at first light blue, changed to green in a minute, and thereafter became brown and finally orange. The crude ethers of alkyl homologs of hydroxyisolapachol, obtained by evaporation of the solvent after reaction with diazomethane, behaved identically; the ether of 2-hydroxy-3-benzoylmethyl-1,4-naphthoquinone gave a deeper and more stable blue.

β-**Phenylethyl**.—The buffer soluble oxidation product from an initial 140 mg. of quinone (solution 3, Table II) on two crystallizations from methanol afforded short prisms of 2-hydroxy-3-benzoylmethyl-1,4-naphthoquinone, m. p. 180–183° (darkening), undepressed by mixture with an authentic sample.

γ-**Cyclohexylpropyl**.—The oxidation product from an initial 100 mg. of quinone (solution 4) separated from the acidified buffer and was collected and crystallized twice from dilute methanol. **2-Hydroxy-3-γ-cyclohexylacetonyl-1,4-naphthoquinone** formed yellow needles, m. p. 178.5–179.5°.

Anal. Calcd. for $C_{19}H_{20}O_4$: C, 73.06; H, 6.45. Found: C, 72.90; H, 6.87.

The compound gave the same color reactions as hydroxyisolapachol with alkali, concentrated sulfuric acid, or with diazomethane followed by alcoholic alkali.

Cyclohexyl.—The buffer soluble oxidation product from an initial 800 mg. of quinone (solution 5) was crystallized twice from ether. The resultant crude solid (91 mg., 15%), recrystallized three times from alcohol, afforded 63 mg. of yellow prisms, m. p. 192.5–194.5° (dec., bath preheated to 180°). Heated slowly from 165°, the compound melted at 181–183° (dec.). The same *substance* was obtained from an oxidation initiated by direct sunlight (solution 6).

Anal. Calcd. for $C_{16}H_{12}O_4$: C, 71.63; H, 4.51. Found: C, 71.76, 71.44; H, 4.82, 4.74.

The substance dissolved in alkali to an orange solution, and in concentrated sulfuric acid with a brown color that turned quickly to blue and then red. No pure product from the action of sulfuric acid could be isolated. The absorption spectrum of the compound, measured with a Baird Infrared Recording Spectrophotometer, Model B, contained a hydroxyl band at 2.93 μ and a single carbonyl band at 5.95 μ. Its methyl ether, m. p. 156–159°, prepared with diazomethane, showed the same carbonyl and no hydroxyl absorption.

Isobutyl.—The buffer soluble material from oxidation of an initial 800 mg. of quinone in diffuse light (solution 7) was precipitated by acid from 40 cc. of alkali and crystallized twice from a large volume of absolute ethanol. There was obtained 10 mg. of sparingly soluble, yellow, microcrystalline powder, dec. 240°, and no other isolable product. The same *substance*, dec. 245–248° (bath preheated to 240°) (found: C, 69.79, 69.31; H, 3.83, 3.38), was obtained in similarly small yield from an oxidation initiated by direct sunlight (solution 8). It dissolves in alkali with a crimson, in concentrated sulfuric acid with an orange color.

The buffer soluble material from an oxidation initiated by direct sunlight of 950 mg. of quinone (solution 8) was precipitated by acid successively from 50 cc. and 75 cc. of dilute alkali. The second precipitate was mainly the substance dec. 240°. The aqueous mother liquors were extracted with ether, which was dried and evaporated;

the residue (120 mg.), after two crystallizations from dilute alcohol, furnished 11 mg. (1%) of 2-hydroxy-3-acetonyl-1,4-naphthoquinone, m. p. 174–176.5°.

The neutral residue from oxidation 8 was washed with petroleum ether and crystallized once from ether and twice from alcohol. There was obtained 21 mg. (3%) of product, m. p. 177–182.5°, that after three crystallizations from alcohol furnished 8 mg. of square plates of β,β-dimethyldihydrofurano-1,4-naphthoquinone, m. p. 185.5–188.5°, undepressed by mixture with authentic material. Alkaline hydrolysis of a 3-mg. sample afforded 2-hydroxy-3-β-hydroxyisobutyl-1,4-naphthoquinone,[20] m. p. 122–123.5°.

γ,γ-Dimethylallyl.—The neutral residue after extraction with 0.01 *N* sodium hydroxide from oxidation of an initial 300 mg. of lapachol (solution 9) was washed with petroleum ether and crystallized from 1 cc. of alcohol. There was obtained 53 mg. (20%) of product, m. p. 139–143.5°, which on one further crystallization afforded orange prisms of dehydro-α-lapachone, m. p. 143–144°, that did not depress the melting point of an authentic sample.

Benzyl.—The buffer soluble oxidation product from an initial 43 mg. of quinone (solution 11) was precipitated by acid from 2 cc. of alkali and crystallized three times from dilute alcohol. There was obtained 3 mg. (7%) of fine, yellow needles, m. p. 155.5–158°, which on two crystallizations from dilute acetic acid gave 2-hydroxy-3-benzoyl-1,4-naphthoquinone, m. p. 161–162°, undepressed by mixture with the synthetic substance.

2-Benzoyl-1-naphthol was prepared[31] in 10–16% yield from 1-naphthol by condensation with benzoic acid in the presence of anhydrous zinc chloride. The substance, which forms long, yellow prisms from alcohol, acetic acid or petroleum ether, appears to be polymorphous,[32] m. p. 64.5–66.5° or 72.5–74°.

A stirred solution of 8.4 g. of 2-benzoyl-1-naphthol in 50 cc. of acetic acid was treated dropwise with 2.3 cc. of concentrated nitric acid in 25 cc. of acetic acid during seven hours, and the suspended solid (6.05 g., m. p. 129–130.5°) collected. Dilution of the mother liquor with water and crystallization of the precipitate from acetic acid furnished 0.95 g. (11%) of 2-benzoyl-1,4-naphthoquinone, m. p. 159–161.5°. The main product, crystallized from 50 cc. of acetic acid, afforded 5.6 g. (56%) of **4-nitro-2-benzoyl-1-naphthol**, m. p. 133–135°. The analytical sample, crystallized from ligroin (b. p. 60–90°) and from alcohol, formed yellow needles, m. p. 132–133°.

Anal. Calcd. for $C_{17}H_{11}O_4N$: C, 69.62; H, 3.78. Found: C, 69.51; H, 3.80.

A solution of 6.4 g. of 4-nitro-2-benzoyl-1-naphthol in 300 cc. of warm acetic acid was shaken with 0.17 g. of platinic oxide (Adams) and hydrogen (25–30 lb.) for twelve hours, evaporated in vacuum, and the residue treated with 25 cc. of acetic anhydride and, after five minutes, 150 cc. of water. The precipitate, collected and recrystallized from 600 cc. of alcohol, afforded 3.75 g. (52%) of **4-acetylamino-2-benzoyl-1-naphthol**, m. p. 248–257°. The analytical sample formed fine, yellow needles, m. p. 255.5–256.5°, readily soluble in dilute alkali.

Anal. Calcd. for $C_{19}H_{15}O_3N$: C, 74.74; H, 4.95. Found: C, 74.91; H, 5.04.

A suspension of 3.3 g. of 4-acetylamino-2-benzoyl-1-naphthol in 30 cc. of acetic acid was treated with 0.7 cc. of concentrated nitric acid. Within two minutes the starting material dissolved with effervescence, and shortly afterward the product separated from solution and was collected after dilution with water. After crystallization from 25 cc. of acetic acid, there was obtained 2.6 g. (92%) of **2-benzoyl-1,4-naphthoquinone**, m. p. 162–163°. The analytical sample formed yellow needles, m. p. 161.5–162.5°, giving a red vat in alkaline sodium hydrosulfite, and in concentrated sulfuric acid a yellow coloration that darkens rapidly to deep green.

Anal. Calcd. for $C_{17}H_{10}O_3$: C, 77.85; H, 3.84. Found: C, 77.74; H, 3.71.

A mixture of 1.5 g. of 2-benzoyl-1,4-naphthoquinone, 5 cc. of acetic anhydride and 2 cc. of boron trifluoride etherate was allowed to stand four days and filtered, and the crystalline orange borofluoride[29] refluxed half an hour in 10 cc. of 85% ethanol for hydrolysis. The solid product, **3,4-diacetoxy-2-benzoyl-1-naphthol**, m. p. 175.5–180°, was obtained in 68% over-all yield. The analytical sample, from acetic acid, formed yellow tablets, m. p. 177.5–178.5°.

Anal. Calcd. for $C_{21}H_{16}O_6$: C, 69.22; H, 4.43. Found: C, 69.67; H, 4.50.

3,4-Diacetoxy-2-benzoyl-1-naphthol was hydrolyzed under nitrogen with 5% alcoholic potassium hydroxide, and the hydroquinone oxidized by acid ferric chloride, followed by alkali and air. Precipitation by acid furnished in 86% yield 2-hydroxy-3-benzoyl-1,4-naphthoquinone, m. p. 162–164.5°. The analytical sample, from 50% acetic acid, formed long, yellow needles, m. p. 163.5–164° (literature[30] 159.5°), which gave yellow solutions in alkali and in concentrated sulfuric acid, and a red-brown vat in alkaline hydrosulfite.

Anal. Calcd. for $C_{17}H_{10}O_4$: C, 73.38; H, 3.62. Found: C, 73.62; H, 3.62.

Summary

A photocatalyzed autoxidation of 3-substituted 2-hydroxy-1,4-naphthoquinones in dilute ether solution has been discovered. In saturated side chains unbranched at the α and β-positions, the β-methylene is transformed to carbonyl.

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(32) Arventi, *Bull. soc. chim.*, [5] **4**, 999 (1937).