[CONTRIBUTION FROM THE DEPARTMENT OF BIOCHEMISTRY, STATE UNIVERSITY OF IOWA]

Oxidation of Hindered 6-Hydroxychromans

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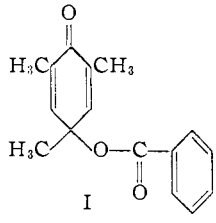
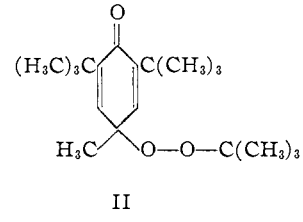
2,2,5,7,8-Pentamethyl-6-hydroxychroman, α-tocopherol and γ-tocopherol have been allowed to react with benzoyl peroxide at 30° for short periods of time. The products isolated have been explained on the basis of free radical interactions.

Introduction

A study on the oxidation of hindered 6-hydroxychromans was undertaken in this Laboratory to obtain data on the mechanism of reaction between the 6-hydroxychroman antioxidants of the vitamin E family and free radicals. Several groups of investigators have studied free radical interactions with hindered phenols, and, in some cases, products consisting of the hindered phenol coupled with the reacted free radical were isolated. Thus, Cosgrove and Waters[3] on allowing benzoyl peroxide to react with mesitol obtained 4-benzoyloxy-2,4,6-trimethylcyclohexa-2,5-dienone (I) as the major product. Campbell and Coppinger[4] found that *t*-butylhydroperoxide reacted with 2,6-di-*t*-butyl-4-methylphenol to give 2,6-di-*t*-butyl-4-butylperoxy-4-methylcyclohexa-2,5-dienone(II) in good yield.

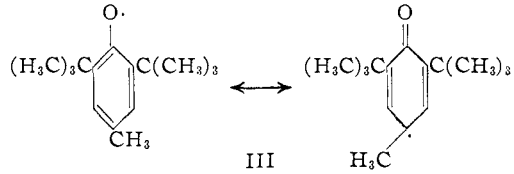


I



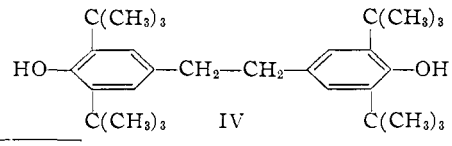
II

These products are explained quite readily as stabilization products of the intermediate phenoxy or isomeric radical III



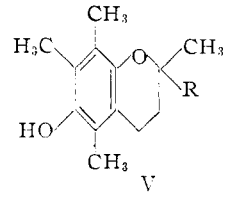
III

with another radical. Other products, such as 1,2-bis-(3,5-di-*t*-butyl-4-hydroxyphenyl)-ethane (IV) are explained less readily as stabilization products of benzyl-free radicals. Recently, however, Cook, Nash and Flanagan[5] have presented excellent evidence for the rearrangement of the 2,6-di-*t*-butyl-4-methylphenoxy radical III to a 2,6-di-*t*-butylbenzyl radical; thus, explanation of dimeric stabilization products of type IV are easily envisaged.

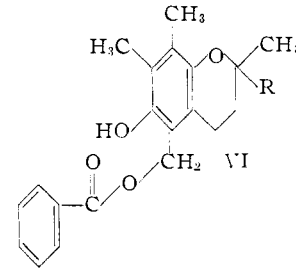


IV

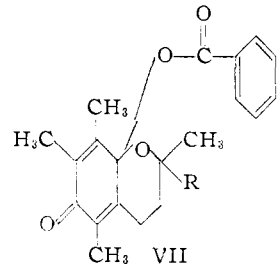
In this study, 2,2,5,7,8-pentamethyl-6-hydroxychroman (Va), α-tocopherol (Vb) and γ-tocopherol were allowed to react with benzoyl peroxide and the resulting oxidation products isolated. On oxidation of Va, an excellent yield of a 6-hydroxychroman benzoate with the most probable structure VIa[6] was obtained and only small amounts of 2,5,6-trimethyl-3-(3′-methyl-3′-hydroxy)-butyl-1,4-benzoquinone (VIIIa). The quinone can be best explained as a hydrolytic product resulting from an intermediate such as VIIa. Any such intermediate would be easily hydrolyzed during the isolation procedure. When α-tocopherol (Vb) was allowed



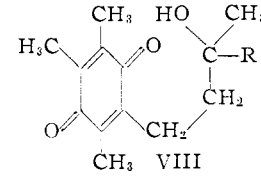
V



VI



VII

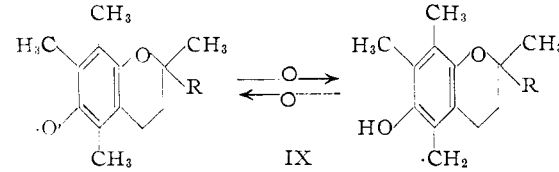


VIII

a, R = $-CH_3$ b, R = $-C_{16}H_{33}$

to react with benzoyl peroxide, 23–53% yields of α-tocoquinone were isolated from the reaction mixtures suggesting an appreciable amount of an intermediate compound VIIb.

These end products, VIIIa, VIIIb and VIa, can be best generalized by assuming an intermediate formation of a 6-hydroxychroman free radical, chromanoxy (IX).



IX

The chromanoxy radical could terminate itself either by formation of an hydrolytic-labile intermediate VII to give quinones VIII or by rearrangement to give a benzyl derivative VI.

Cook[5] has noted that the more stable phenoxy

(1) Abstracted from a thesis submitted by this author in partial fulfillment of the requirements for the degree of Doctor of Philosophy, State University of Iowa, August, 1952.

(2) Deceased March 30, 1953.

(3) S. L. Cosgrove and W. A. Waters, *J. Chem. Soc.*, 388 (1951).

(4) T. W. Campbell and G. M. Coppinger, THIS JOURNAL, **74**, 1469 (1952).

(5) C. D. Cook, N. G. Nash and H. R. Flanagan, *ibid.*, **77**, 1783 (1955).

(6) However, the C-7 positional isomer of VIa cannot be eliminated.

free radicals have *ortho* and *para* substituents which lack hydrogen atoms. Such radicals are said to be capable of independent existence for a period of several hours and exhibit highly colored solutions as well as being dissociated in the crystalline state. On the other hand, a compound having an hydrogen atom on the *ortho* and/or *para* substituents developed a transient deep colored solution that was rapidly masked by the color of the oxidation product. Thus, it was interesting to note in our work that a transient deep olive green colored solution was observed and was rapidly masked by the orange color of the oxidation products, indicating to us that the intermediate radicals have only a transitory existence.

γ-Tocopherol on oxidation with benzoyl peroxide gave the red quinone, 2,7,8-trimethyl-2-(4′,8′,-12′ - trimethyltridecyl - 1) - chroman - 5,6 - quinone. This supplements evidence indicating γ-tocopherol as the precursor of the red quinone in autoxidizing cottonseed oil[7] and further illustrates the vulnerability of the C-5 position of the tocopherol molecule.

Experimental[8]

Materials.—Commercial benzoyl peroxide was purified by the method of Cass.[9] Bis-(*m*-chlorobenzoyl) peroxide was prepared by the procedure of Blomquist and Buselli.[10] The purity of the α-tocopherol[11] and γ-tocopherol[12] were assured by infrared spectra. 2,2,5,7,8-Pentamethyl-6-hydroxychroman was prepared by treating isoprene with trimethylhydroquinone.[13]

Reaction of Benzoyl Peroxide with 2,2,5,7,8-Pentamethyl-6-hydroxychroman

2,2,7,8-Tetramethyl-5-benzoyloxymethyl-6-hydroxychroman.—In a 50-ml. erlenmeyer flask 1.90 g. (8.62 mmoles) of 2,2,5,7,8-pentamethyl-6-hydroxychroman in 10 ml. of benzene was stirred with 2.09 g. (8.62 mmoles) of benzoyl peroxide in 15 ml. of benzene, and the resulting solution was allowed to stand for 2 hours under a nitrogen atmosphere. Diethyl ether was added to the solution, and the resulting white crystals were collected on a filter, 1.95 g. On trituration with ether and collecting on a filter, 1.83 g. (62% yield) of white crystals was obtained, m.p. 125–126°.

Anal. Calcd. for $C_{21}H_{24}O_4$: C, 74.09; H, 7.11. Found: C, 73.84; H, 7.11.

Infrared spectrum: 3.08 μ (hydroxyl), 5.97 μ (ester).

Ultraviolet spectrum: $\lambda_{max.}$ 301 mμ (ε 4,000).

The yellow ether filtrate was washed with 10% potassium carbonate solution and dried over anhydrous sodium sulfate. The ether was removed *in vacuo*, and the yellow oil passed over a 25 × 100 mm. Brockmann alumina column developed with Skellysolve B. A stationary brown and a mobile yellow colored band were observed on the column. The brown colored band section was eluted with aqueous ether. On removal of the ether, 120 mg. of a brown colored oil having an infrared spectrum comparable to 2,5,6-trimethyl-3-(3′-methyl-3′-hydroxy)-butyl-1,4-benzoquinone was obtained.

Anal. Calcd. for $C_{14}H_{20}O_3$: C, 71.16; H, 8.53. Found: C, 71.82; H, 8.25.

Reaction of α-Tocopherol with Benzoyl Peroxide

Oxidation.—A typical run consisted of mixing in a 50-ml. erlenmeyer flask, 720 mg. (1.9 mmoles) of α-tocopherol in 8 ml. of anhydrous, thiophene-free benzene with 700 mg. (2.9 mmoles) of benzoyl peroxide in 12 ml. of benzene. The reaction mixture was allowed to stand for 30 minutes in a 30° water-bath and then was poured into water. The solution was adjusted to *p*H 7 with 1 *N* potassium hydroxide and then extracted with diethyl ether. The aqueous solution was evaporated *in vacuo*, and a *p*-phenylphenacyl benzoate was prepared.[14] It was recrystallized from ethanol; m.p. 169–171°; mixed m.p. with an authentic sample was 169–171°. Another run indicated 75% benzoic acid by titration produced after the reaction mixture was allowed to stand for 10 minutes. No carbon dioxide was evolved during these reactions as determined by experiments in Warburg vessels. α-Tocopheryl acetate did not react with benzoyl peroxide under these conditions.

α-Tocoquinone.—The ether extract obtained from the reaction described above was dried over anhydrous sodium sulfate. After the ether had been removed *in vacuo*, the yellow colored oil was dissolved in Skellysolve B and passed over a 25 × 100 mm. alumina column (Brockmann, Merck and Company, Inc.). The yellow colored band was separated and eluted with aqueous diethyl ether to give 200 mg. (23% yield) of α-tocoquinone.[15]

Anal. Calcd. for $C_{29}H_{48}O_3$: C, 78.32; H, 10.88. Found: C, 78.55; H, 10.69.

An α-tocohydroquinone di-*m*-chlorobenzoate derivative was prepared from a 259-mg. α-tocoquinone fraction by reduction with 10 g. of sodium hydrosulfite and 2.0 g. of sodium hydroxide and acylation with 250 mg. of *m*-chlorobenzoyl chloride. The flask was shaken for 1 hour, and then the solution was extracted with diethyl ether to give 140 mg. of yellow colored amorphous solid.

Anal. Calcd. for $C_{43}H_{58}O_5Cl_2$: C, 71.15; H, 8.05. Found: C, 70.72; H, 8.39.

Infrared spectrum: 5.77 μ (ester), 6.37 μ (conjugated ring), and 13.52 μ (chlorobenzene ring).

Compound A.—This compound was obtained from alumina column eluates after removal of the Skellysolve B *in vacuo*. From the 1.9 mmoles α-tocopherol oxidation, 200 mg. (23% yield) of yellow colored oil was obtained, $n^{31}D$ 1.4992. A 20-mg. sample (0.045 mmole) liberated iodine from an acetic acid solution of potassium iodide. Quantitative estimation of the iodine gave a value of 0.038 meq.[16]

Anal. Calcd. for $C_{29}H_{50}O_3$: C, 77.97; H, 11.28. Found: C, 77.91; H, 10.84.

Ultraviolet spectrum: $\lambda_{max.}$ 246 mμ (ε 19,100) and λ_{max} 238 mμ (ε 19,100).

Infrared spectrum: 5.97 μ (dienone), 6.06 μ (double bond), 6.29 μ (conjugation), 8.02 and 9.18 μ (ether, chroman), 10.4 μ (peroxide, epoxide, or tertiary C–O vibration).[17]

Molecular weight: a value of 467 was obtained by the ebullioscopic method of Menzies and Wright.

Reaction of α-Tocopherol with Bis-(*m*-Chlorobenzoyl) Peroxide

Oxidation.—In a 50-ml. erlenmeyer flask 1.97 g. (4.58 mmoles) of α-tocopherol in 12 ml. of benzene was mixed with 1.43 g. (4.58 mmoles) of bis-(*m*-chlorobenzoyl) peroxide in 18 ml. of benzene and the reaction mixture was allowed to stand at 30° for 30 minutes. When the peroxide solution

(7) C. E. Swift, G. E. Mann and G. S. Fisher, *Oil and Soap*, **21**, 317 (1944).

(8) A Perkin–Elmer Model 21, double-beam spectrophotometer with sodium chloride prisms was used for recording the infrared spectra. A spacer was made of aluminum foil, 17.6 μ thick. The ultraviolet data were obtained by a recording Cary on samples dissolved in isooctane. Microanalyses were obtained from the Clark Microanalytical Laboratory, Urbana, Illinois.

(9) W. E. Cass, THIS JOURNAL, **68**, 1976 (1946).

(10) A. T. Blomquist and A. J. Buselli, *ibid.*, **73**, 3883 (1951).

(11) The DL-α-tocopherol employed in these studied was kindly supplied by Merck and Company, Inc., Rahway, N. J.

(12) The D-γ-tocopherol was obtained from Distillation Products, Inc., Rahway, N. J.

(13) L. I. Smith, H. E. Ungnade, H. H. Hoehn and S. Wawzonek, *J. Org. Chem.*, **4**, 311 (1939).

(14) R. L. Shriner and R. C. Fuson, "The Systematic Identification of Organic Compounds," John Wiley and Sons, Inc., New York, N. Y., 3rd ed., 1948, p. 157.

(15) A 42% yield of α-tocoquinone was obtained from a reaction mixture which was allowed to stand 15 minutes $n^{31}D$ 1.4958. When glacial acetic acid was used as the solvent, a 52% yield of α-tocoquinone was obtained. These samples had infrared spectra which were identical in every respect with that of authentic α-tocoquinone.

(16) α-Tocopheroxide (P. D. Boyer, THIS JOURNAL, **73**, 733 (1951)) liberated iodine from an acidic sodium iodide solution to the extent of 57%. It is conceivable that α-tocopheroxide and Compound A may be isomeric, but they cannot be identical as shown by infrared and ultraviolet absorption spectra comparisons.

(17) A. R. Philpotts and W. Thain, *Anal. Chem.*, **24**, 638 (1952).

was mixed with the α-tocopherol solution, an olive green coloration developed immediately and then faded to a brilliant yellow color in approximately 20 seconds. The benzene solution was concentrated *in vacuo*, and 0.53 g. of *m*-chlorobenzoic acid was collected on a filter. Another 0.16-g. sample was obtained by 0.5 *N* sodium bicarbonate extraction. On admixture with authentic *m*-chlorobenzoic acid, no depression of melting point was observed, m.p. 152–153°.

α-Tocoquinone.—The hydrocarbon layer from the above run was worked up as described in the previous section for α-tocoquinone. A 520-mg. sample (25%) was obtained which had an infrared spectrum identical with that obtained from a pure sample of α-tocoquinone.

Compound A.—From the yellow colored eluates from the alumina column, 410 mg. (20% yield) of compound A was obtained which had an infrared spectrum identical with that which was obtained above.

Compound B.—When 1.60 g. (5.15 mmoles) of bis-(*m*-chlorobenzoyl) peroxide in 20 ml. of benzene was mixed with 2.22 g. (5.15 mmoles) of α-tocopherol in 10 ml. of benzene and allowed to stand 15 minutes under a flow of nitrogen. When the reaction mixture was separated as previously described, 310 mg. (14% yield) of a slightly yellow colored oil, $n^{30}D$ 1.5134, was obtained from the forerun eluates. It had a molecular weight[14] of 448 and was insoluble in methanol and ethanol but readily soluble in non-polar solvents. It gave no reaction with acidic sodium iodide solution, saturated sodium hydrosulfite solution, or ferric chloride dipyridyl reagent (Emmerie and Engel test).

Anal. Calcd. for $C_{29}H_{48}O_2$: C, 81.25; H, 11.29. Found: C, 81.28; H, 11.56.

Ultraviolet spectrum: λ_{max}. 293 mμ (ε 2,150).

Infrared spectrum: 5.84 μ (carbonyl), 6.10 μ (double bond), 8.02 and 9.25 μ (ether).

Reaction of Benzoyl Peroxide with α-Tocopherol: 2,7,8-Trimethyl-2-(4′,8′,12′-trimethyltridecyl-1)-chroman-5,6-quinone.—In a 50-ml. erlenmeyer flask 0.80 g. (1.92 mmoles) of α-tocopherol was dissolved in 7 ml. of benzene, and to this solution a 0.46-g. (1.92 mmoles) solution of benzoyl peroxide in 10 ml. of benzene was added. The flask was stoppered and allowed to stand for 40 minutes. The solution was washed with 10% potassium carbonate, water and dried over sodium sulfate. After removal of the solvent, the red oil was poured on a 25 × 100 mm. Brockmann alumina column and developed with Skellysolve B. The large red band section was eluted with water and ether. On removal of the ether, 0.50 g. of red oil was obtained that had several absorption bands in the infrared in common with β-lapachone.

Anal. Calcd. for $C_{28}H_{46}O_3$: C, 78.08; H, 10.77. Found: C, 77.55; H, 11.32.

Acknowledgment.—The authors are grateful to Procter and Gamble Company for liberal financial support.

IOWA CITY, IOWA

[CONTRIBUTION FROM THE MOORE LABORATORY OF CHEMISTRY, AMHERST COLLEGE]

7-Azaindole. II. Conversion to 7-Methyl-7H-pyrrolo[2,3-b]pyridine and Related Compounds[1,2]

BY MICHAEL M. ROBISON AND BONNIE L. ROBISON

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Treatment of 7-azaindole (I) with methyl *p*-toluenesulfonate produced 7-methyl-1H-pyrrolo[2,3-b]pyridinium *p*-toluene sulfonate (IIa), which, on treatment with aqueous base, loses the elements of *p*-toluenesulfonic acid to form 7-methyl-7H-pyrrolo[2,3-b]pyridine (III). The structure of III was proved by catalytic hydrogenation and hydrogenolysis to 1-methyl-3-(2-aminoethyl)-piperidine (IV), which was identified as 1-methyl-3-[2-(1-(3-phenyl)-ureido)-ethyl]-piperidine (V). The urea was prepared for comparison by an independent synthesis from 3-(2-aminoethyl)-pyridine. The yellow 7H-pyrrolopyridine is a comparatively strong base, unlike the colorless 1-methyl-7-azaindole (VI, 1-methyl-1H-pyrrolo[2,3-b]pyridine), which was prepared by methylation of the sodio derivative of 7-azaindole with methyl iodide. Treatment of either compound III or VI with methyl iodide produces 1,7-dimethyl-1H-pyrrolo[2,3-b]pyridinium iodide (VII). Several new derivatives of 2-methylamino-3-picoline and of 3-(2-aminoethyl)-pyridine and an improved procedure for the large-scale preparation of 7-azaindole are also described.

2-Aminopyridine on treatment with methyl iodide is methylated at the ring nitrogen to produce N-methyl-2-pyridonimine hydroiodide, which, on reaction with silver oxide or aqueous alkali, loses the elements of hydriodic acid to form N-methyl-2-pyridonimine. If, on the other hand, the amine is converted to its sodio derivative by the action of sodium amide in ether before the methylating agent is added, substitution occurs at the amino nitrogen.[3] In view of the structural relationship of 7-azaindole (I) to 2-aminopyridine, it seemed of interest to determine whether methylation reactions would take a similar course with the bicyclic compound. This was found to be the case. When 7-azaindole was treated with a refluxing benzene solution of methyl *p*-toluenesulfonate, methylation took place at the 7-position to produce 7-methyl-1H-pyrrolo[2,3-b]-pyridinium *p*-toluenesulfonate (IIa) in high yield. Treatment of the salt with base converted it to a hygroscopic yellow substance which was shown to be 7-methyl-7H-pyrrolo[2,3-b]pyridine (III).

The ultraviolet spectrum of the yellow compound is very different from the spectra of the 1H-pyrrolo[2,3-b]pyridines. In cyclohexane the compound exhibits a third absorption maximum at 385 mμ. In aqueous alkali the yellow color persists but the intensity is lower and the compound loses its color as the acidity of the medium is increased. In 10^{-3} *N* acid, 7-azaindole and the 7-methyl compound have similar spectra (Fig. 1), as would be ex-

(1) This investigation was supported in part by a research grant, number C-2574 from the National Cancer Institute of the National Institutes of Health, Public Health Service.

(2) Paper I of this series: M. M. Robison and B. L. Robison, THIS JOURNAL, **77**, 457 (1955).

(3) A. E. Chichibabin, R. A. Konowalowa and A. A. Konowalowa, *Ber.*, **54**, 814 (1921).