The Photochemical Transformation of Some *p*-Quinol Ethers[1]

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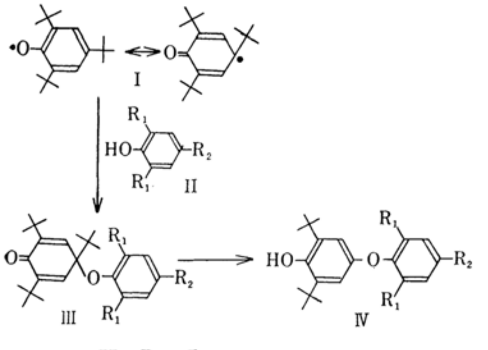
In our previous reports on the biosynthetic mechanism of thyroxine formation, several quinol ethers III were synthesized by the tri-*t*-butylphenoxy radical I with analogs II of diiodotyrosine.[3,4] Some of these quinol ethers were also converted into analogs IV of thyroxine by reaction with acid or by pyrolsis. This sequenece of reactions represents a complete model for the mechanism by which, according to Johnson and Tewkesbury,[5] thyroxine is synthesized from two molecules of diiodotyrosine *in vivo*. On the basis of the assumption that quinol ethers of type III may be converted into analogs of thyroxine by ultraviolet irradiation, we initiated the photochemical reactions of these quinol ethers. A preliminary investigation of the photoreaction of the quinol ether (III: $R_1=H$, $R_2=(CH_2)_2COOEt$) gave quite complex results.



$R_1=H$; Br ; I
$R_2=(CH_2)_2COOC_2H_5$; $CH_2CH(NH_2)COOH$, etc.

Therefore, the quinol ether V[6] was chosen as the first compound to be studied in the systematic investigation of the photochemical behavior of such quinol ethers.

The irradiation of the quinol ether V[6] in methanol under bubbling nitrogen gave a photoketone $C_{19}H_{32}O_2$ (VI), isomeric to V, in an 11% yield and tri-*t*-butylphenol (VII) in a 3% yield. The photoketone VI was characterized as a conjugated enone from its ultraviolet spectrum (λ_{max} 248 and 282 mμ) and its infrared spectrum (1650 and 1630 cm^{-1}). The structure of VI was indicated by its NMR spectrum (Table I), which consists of four groups of peaks, and by considering the analogous transformation of 2, 5-cyclohexadienones into "photoketones" with bicyclo [3, 1, 0] hex-2-ene-1-one structures.[7,8] Three peaks, at $\tau=9.07$, 8.81 and 8.75, and a singlet at $\tau=6.40$ are readily assigned to the three *t*-butyl groups and a methoxyl group respectively. Two other doublets, at $\tau=7.03$ and 3.67, are attributed to an allylic proton on a cyclopropane ring conjugated with a double bond[9] and to a proton of a double bond. The spin-spin coupling constant ($J=$ 6 c.p.s.) of these doublets suggests that these two protons may be adjacent to each other.

On the other hand, the irradiation of V in ether gave a crytalline photophenol $C_{15}H_{24}O_2$ (VIII) in a 10% yield, in addition to a small amount of VI. The dealkylation of this phenol with aluminum chloride in hot benzene yielded pyrocatechol. The NMR spectrum of VIII shows the presence of two adjacent protons on a benzene ring (AB type quartet, centering at $\tau=3.27$; $J=8.5$ c.p.s.). The infrared spectrum (815 cm^{-1}) also indicates two adjacent hydrogen atoms on a benzene ring. Therefore, it follows that the structure of the photophenol is represented by the formula VIII, VIIIa, or VIIIb. Among these three formulae, the structure VIII is assigned to the photophenol by considering that the minimum rearrangement has occurred, and by reasoning on the basis of a pre-considered mechanism.

In the presence of oxygen, the irradiation of V in ether gave the photophenol VIII and a crystalline product (IX) $C_{19}H_{32}O_4$ in an 11% yield. The hydroperoxyl nature of IX was

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[3] T. Matsuura and H. J. Cahnmann, *J. Am. Chem. Soc.*, **82**, 2055 (1960).

[4] T. Matsuura and A. Nishinaga, *J. Org. Chem.*, **27**, 3072 (1962).

[5] T. B. Johnson and L. B. Tewkesbury, Jr., *Proc. Natl. Acad. Sci. U. S.*, **28**, 73 (1942).

[6] E. Müller, K. Ley and W. Kiedaisch, *Chem. Ber.*, **87** 1605 (1954).

[7] a) D. H. R. Barton, P. de Mayo and M. Shafiq, *J. Chem. Soc.*, **1958**, 140; b) D. Arigoni, H. Bosshard, H. Bruderer, G. Büchi, O. Jeger and L. J. Krebaum, *Helv. Chim. Acta*, **40**, 1732 (1957).

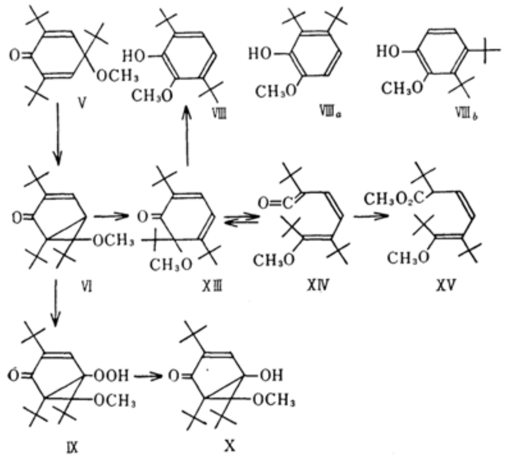
[8] H. E. Zimmerman and D. I. Schuster, ibid., **83**, 4486 (1961); **84**, 4527 (1962).

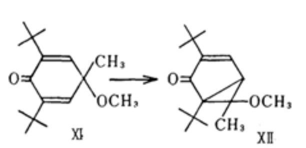
[9] R. Huisgen and G. Juppe, *Chem. Ber.*, **94**, 2332 (1961).

TABLE I. CHEMICAL SHIFTS AND SPIN-SPIN COULING CONRTANTS*

Compound	Chemical shifts[a)] of protons				
	t-Butyl	Methoxyl	Vinyl	Cyclopropyl	Others
V[b)]	9.08 s (9) 8.77 s (18)	6.88 s (3)	3.55 s (3)	—	—
VI[b)]	9.07 s (9) 8.81 s (9) 8.75 s (9)	6.40 s (3)	3.67 d (1) (J=6 c.p.s.)	7.03 d (1) (J=6 c.p.s.)	—
VIII[b)]	8.62 s (18)	6.21 s (3)	3.27 q (2)[d)] (J=8.5 c.p.s.)	—	4.45 s (1)[e)]
IX[c)]	9.01 s (9) 8.75 s (9) 8.67 s (9)	6.00 s (3)	3.58 s (1)	—	2.03 s (1)[f)]
X[c)]	9.03 s (9) 8.77 s (9) 8.67 s (9)	6.15 s (3)	3.70 s (1)	—	7.93 s (1)[e)]
XII[b)]	8.92 s (9) 8.88 s (9)	6.96 s (3)	3.17 d (1) (J=3.5 c.p.s.)	8.02 d (1) (J=3.5 c.p.s.)	8.45 s (3)[g)]
XI[b)]	8.78 s (18)	6.97 s (3)	3.70 s (1)	—	8.70 s (3)[g)]

* The NMR spectra were taken in a Varian A-60. a) τ-values: internal TMS reference. s, singlet; d, doublet; q, quartet. Proton numbers in parentheses. b) Taken in carbon tetrachloride (ca. 5% solution). c) Taken in deuteriochloroform (ca. 5% solution). d) Aromatic protons. e) Hydroxyl proton. f) Hydroperoxyl proton. g) Methyl protons.





confirmed by the reaction with potassium iodide to yied two equivalents of iodine and a hydroxyl compound (X), $C_{19}H_{32}O_3$. The ultraviolet spectra of IX (λ_{max} 237 and 285 mμ) and of X (λ_{max} 237 and 256.5 mμ; λ_{infl} 290 mμ) and the infrared spectra of IX (1665 and 1625 cm^{-1}) and of X (1660 and 1630 cm^{-1}) indicate the presence of a conjugated enone. The NMR spectrum of IX shows no peak corresponding to a cyclopropane proton conjugated with the double bond, but it does show a singlet at τ=2.03, which is assigned to a hydroperoxyl proton. In this case, the peak attributed to the double bond proton (τ=3.58) is not split. We can thus formulate the hydroperoxide and the hydroxy compound as IX and X respectively. The formation of the hydroperoxide can be explained the photo-induced allylic oxidation[10)] of the photoketone VI.

The irradiation of the quinol ether XI[11)] in ether gave a crystalline photoketone XII in an 11% yield, whereas irradiation in methanol did not give crystalline products. The structure is assigned to the formula XII by the interpretation of its NMR spectrum, which is similar to that of VI (Table I). The photoketone is unstable, and, on standing for several weeks, it liquefied to form a unidentified product.

Recently Zimmerman and Schuster proposed a mechanism for the photochemical rearrangement of 4, 4-diphenylcyclohexa-2, 5-dienone.[8)] This mechanism involves the $n \rightarrow \pi^*$ excitation of the cyclohexadienone system as the initiating step, and it can also account for the formation of VI, VIII and XII. The fact that the phenol VIII is not formed on the irradiation of V in methanol may be due to the conversion of XIII, under these conditions, into the ester XV via the ketene XIV.[12)]

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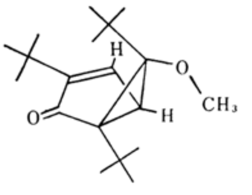
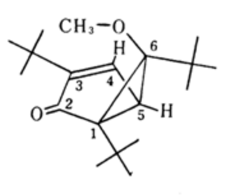
10) E. H. Farmer and D. A. Sutton, *J. Chem. Soc.*, **1943**, 120.

11) G. M. Coppinger and T. W. Campbell, *J. Am. Chem. Soc.*, **75**, 734 (1953).

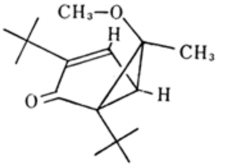
12) D. H. R. Barton and G. Quinkert, *J. Chem. Soc.*, **1960**, 1.



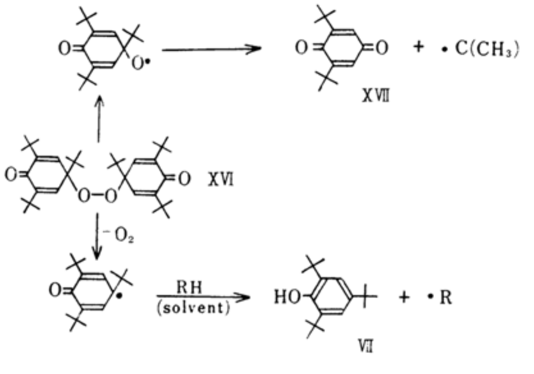
VI$_a$



VI$_b$



XII$_a$



We wish also to discuss the stereochemistry of the photoketone VI. Of two possible stereochemical structures, VIa and VIb,[13] VIa with an *exo*-methoxyl group was tentatively assigned to the photoproduct for the following reasons: i) A stereomodel for VIb demonstrates that the two *cis*-*t*-butyl groups of the cyclopropane ring strongly hinder each other, whereas the trans arrangement of the *t*-butyl groups in VIa is sterically more favored. ii) The NMR peak of the methoxyl protons of the starting dienone V (τ=6.88) and also of XI (τ=6.97) is located at a higher magnetic field than is usual for methoxyl protons. This shows that these protons must be shielded by the dienone system. It seems, therefore, very likely that this shielding is cancelled in the *exo*-configuration of the methoxyl group (τ=6.40) of VIa. iii) The unusual downward shift (τ=6.15) of the methoxyl peak of the hydroxy compound X suggest that the methoxyl group is sterically close to the hydroxyl group,[14] that, namely, both groups are cis. This argument is also applicable to the hydroperoxide IX (methoxyl protons, τ=6.00), whose precursor is considered to be VI.

On the other hand, the methoxyl protons (τ=6.96) of XII are apparently much shielded by the enone system. This shows that XII may have the stereochemical structure XIIa,[13] with an *endo*-methoxyl group.

The irradiation of the peroxide XVI[15] in petroleum ether gave two crystalline products; one was identified as tri-*t*-butylphenol (VII) (13% yield), and the other as 2,6-di-*t*-butyl-*p*-benzoquinone (XVII) (48% yield). The formation of these products can be formulated as follows:

Experimental[16]

Photolysis was carried out in a cylindrical vessel, into which a 60 W. low-pressure mercury lamp (spiral type) had been inserted; during irradiation, a nitrogen stream was bubbled through a sintered glass disk jointed at the bottom of the vessel.

The Photolysis of 2, 4, 6-Tri-*t*-butyl-4-methoxycyclohexa-2, 5-dienone (V).—*In Methanol.*—A solution of 4.0 g. of the quinol ether V[6,17] in 160 ml. of absolute methanol was irradiated at 35~40°C under bubbling nitrogen for 7 hr. The progress of the reaction was followed by the decrease of an ultraviolet absorption maximum at 248 mμ and by the appearance of a new maximum at about 280 mμ. The mixture was evaporated under reduced pressure. The residual liquid was dissolved in petroleum ether and chromatographed on a containing 100 g. of neutralized alumina (activity 1). Elution with 100 ml. of petroleum ether yielded 1.43 g. of a pale yellow liquid (A) which deposited 0.44 g. (11%) of crystals. Recrystallization from methanol gave 0.31 g. (7.8%) of the photoketone VI as colorless plates (m. p. 87~87.5°C). IR spectrum (Nujol): 1650, 1630, 1595 cm^{-1}. λ_{max}^{EtOH} 248 mμ (ε, 7780) and 282 mμ (ε, 3070).

Found: C, 78.00; H, 11.01. Calcd. for $C_{19}H_{32}O$: C, 78.03 H, 11.03%.

The fractional recrystallization of the residue from the mother liquor yielded 0.09 g. (3%) of colorless prisms (m. p. 129~130°C), which were identified as 2, 4, 6-tri-*t*-butylphenol (VII) (mixture melting point and infrared spectrum). The other products were not obtained in a pure form.

In Ether.—A solution of 4.0 g. of the quinol ether V in 100 ml. of absolute ether was irradiated at 36°C under bubbling nitrogen for 29 hr. The solvent was removed under reduced pressure, and the residual liquid was dissolved in petroleum ether and chromatographed through a column containing 80 g. of neutralized alumina. Elution with 150 ml.

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[13] Each one enantiomeric structure was given for VIa, VIb and XIIa.

[14] Y. Kawazoe, Y. Sato, N. Natsume, H. Hasegawa, T. Okamoto and K. Tsuda, *Chem. Pharm. Bull.* (*Japan*), **10**, 338 (1962).

[15] C. D. Cook and R. C. Woodworth, *J. Am. Chem. Soc.*, **75**, 6242 (1953).

[16] Melting points were determined in capillary tubes and are uncorrected. The infrared spectra were measured with a Nippon Bunko recording spectrophotometer, Model IR-S. The ultraviolet spectra were measured with a Hitachi recording spectrophotometer, Model EPS-2. The microanalyses were made by Mr. J. Goda and his associates of this Faculty.

[17] The starting materials, 2, 4, 6-tri-*t*-butylphenol and 2, 6-di-*t*-butyl-*p*-cresol, for the preparation of V, XI and XVI, were kindly supplied by the Koppers Co., Inc.

of petroleum ether yielded 3 g. of a yellow liquid (A). Elution with petroleum ether and then with benzene yielded 0.98 g. of a liquid which crystallized on standing. Recrystallization from petroleum ether at -70°C gave 0.33 g. of the photophenol VII as needles (m. p. 86.5~87.5°C). These crystals were further purified by sublimation at 75~80°C/5 mmHg to give colorless plates (m. p. 87~88°C). IR spectrum (Nujol): 3350, 1610, 815 cm^{-1}. λ_{max}^{EtOH} 209 mμ (ε, 16900) and 278 mμ (ε, 2360).

Found: C, 76.42; H, 10.33. Calcd. for $C_{15}H_{24}O_2$: C, 76.22; H, 10.24%.

This substance gave a positive phenol reaction with a ferric chloride-ferricyanide reagent.[18] The yellow liquid (A) was distilled at 115~118°C/1 mmHg to give a yellow liquid (n_D^{21} 1.4925). The chromatography of the liquid on an alumina column yielded a few milligrams of plates (m. p. 87~87.5°C), which were identified as the bicyclic enone VI by a comparison of the infrared spectra.

In Ether in the Presence of Air.—A solution of 1.50 g. of the quinol ether V in 100 ml. of absolute ether was irradiated at 36°C under bubbling air for 4 hr. The reaction mixture was evaporated under reduced pressure. The residue was dissolved in petroleum ether and chromatographed on a column containing 40 g. of neutralized alumina. Elution with 80 ml. of petroleum ether yielded 0.78 g. of a liquid containing crystals. The hydroperoxide IX, insoluble to petroleum ether, was collected by filtration. It had a m. p. of 145 °C decomp.; yield, 0.175 g. (10.5%). Recrytallization from ether and petroleum ether gave colorless prisms (m. p. 146°C, decomp.). IR spectrum (Nujol): 3350, 1665, 1625, 1595 cm^{-1}. λ_{max}^{EtOH} 237 mμ (ε, 6680), and λ_{infl}^{EtOH} 285 mμ (ε, 2630).

Found: C, 70.52; H. 10.03. Calcd. for $C_{19}H_{32}O_4$: C, 70.33; H, 9.94%.

This substance turned yellow under diffused light.

Elution with benzene and then with methanol yielded 0.40 g. of a liquid which crystallized on standing. Recrystallization from petroleum ether gave 20 mg. (2%) of colorless needles (m. p. 87~88°C), which were identical with an authentic sample of the photophenol VIII (mixture melting point).

In another run, the hydroperoxide IX and the phenol VIII were isolated in 7.5% and 13% yields respectively.

The Dealkylation of the Photophenol VIII.—A solution of 60 mg. of the photophenol VIII in 10 ml. of dry benzene was heated under reflux with 1 g. of powdered anhydrous aluminum chloride. The mixture was then treated with ice-water and extracted with ether. The ethereal layer was washed with water, dried over anhydrous sodium sulfate, and evaporated. Recrystallization of the residue from benzene gave 10 mg. (36%) of plates (m. p. 103~105°C), which were identical with catechol (mixture meeting point and infrared spectrum).

The Reduction of the Hydroperoxide IX to X.—A solution of 64 mg. of the hydroperoxide in 4 ml. of acetic acid was mixed with a solution of 300 mg. of sodium iodide in 3 ml. of acetic acid. The mixture was then warmed at 50°C for 5 min. After dilution with water, the iodine which had been liberated was titrated with 3.50 ml. (corresponding to 0.89 atom oxygen) of a 0.101 N sodium thiosulfate solution. The separated solid was collected by filtration, dried (52 mg.), and recrystallized from ether and petroleum ether to give 38 mg. of the hydroxy compound X as colorless plates (m. p. 147~148.5°C). IR spectrum (Nujol): 3510 (with 3600 infl.), 1660, 1630, 1585 cm^{-1}. λ_{max}^{EtOH} 237 mμ (ε, 5480) and 256.5 mμ (ε, 4780), $\lambda_{infl.}^{EtOH}$ 290 mμ (ε, 2290).

The Photolysis of 2, 6-Di-*t*-butyl-4-methoxy-4-methylcyclohexa-2, 5-dienone (XI).[10,17] — *A) In Ether.*—A solution of 4.0 g. of the quinol ether XI in 160 ml. of absolute ether was irradiated at 36°C under bubbling nitrogen for 6 hr. The solvent was then removed under reduced pressure. The residue was dissolved in petroleum ether and chromatographed on a column containing 100 g. of neutralized alumina. Elution with 300 ml. of petroleum ether yielded 2.0 g. of a yellow liquid which did not crystallize. Elution with petroleum ether, benzene, and then ether yielded 1.13 g. of a yellow liquid which partly crystallized on standing.

After digestion with a small amount of petroleum ether, crystals (0.43 g.; 11%) were collected by filtration and recrystallized from petroleum ether at -70°C to give XII as colorless prisms, m. p. 69~70°C. IR spectrum (Nujol): 1695, 1612 cm^{-1}. λ_{max}^{EtOH} 278 mμ (ε, 2860) and λ_{infl}^{EtOH} 235 mμ (ε, 2550).

Found: C, 76.55; H, 10.27. Calcd. for $C_{16}H_{26}O_2$: C, 76.75; H, 10.47%.

This substance, on standing for several weeks, decomposed to give a yellow liquid whose infrared spectrum showed a broad band centering 1700 cm^{-1} and a broad hydroxyl band near 3200 cm^{-1}.

B) In Methanol.—A solution of 4 g. of the quinol ether XI in 160 ml. of absolute methanol was irradiated under bubbling nitrogen and cooling with tap water for 9 hr. The mixture was treated as described in A). Elution of the chromatogram with 200 ml. of petroleum ether yielded 0.89 g. of an orange liquid which crystallized on standing. Recrystallization from methanol gave 0.28 g. of colorless prisms (m. p. 68~70°C) which were identical with an authentic sample of 2, 6-di-*t*-butyl-*p*-cresol (infrared spectrum). Further elution yielded an orange liquid which did not crystallize.

The Photolysis of Bis(1, 3, 5-tri-*t*-butyl-2, 5-cyclohexadien-4-one) Peroxide (XVI).[15,17]—A solution of 4.0 g. of the peroxide XVI in 160 ml. of petroleum ether was irradiated under bubbling nitrogen and cooling with tap water for 12 hr. The solution showed a greenish yellow color during irradiation. The solvent was removed under reduced pressure. The residue, on treatment with 10 ml. of methanol, deposited some crystals which were collected by filtration. Yield, 0.64 g. (16% recovered); m. p. 139~142°C. The melting point was not depressed on admixture with the starting peroxide XVI. The filtrate was evaporated under reduced pressure, and the residue was dissolved in petroleum ether and chromatographed on a column

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[18] G. M. Barton, R. S. Evans and J. A. F. Gardner, *Nature*, **170**, 249 (1952).

containing 40 g. of neutral alumina. Elution with 450 ml. of petroleum ether yielded 0.40 g. (13%) of colorless crystals (m. p. 129∼131°C), which were identified as 2, 4, 6-tri-*t*-butylphenol (VII) (infrared spetrum).

Elution with 50 ml. of a mixture of petroleum ether and benzene (1 : 1) yielded 0.9 g. of a yellow liquid which did not crystallize. Further elution with the same solvent mixture and then with benzene yielded 1.22 g. (48%) of orange crystals (m. p. 67∼68°C), the infrared spectrum of which was identitcal with that of 2, 6-di-*t*-butylbenzoquinone (XVII).[19]

Summary

The ultraviolet irradiation of 2, 4, 6-tri-*t*-butyl-4-methoxycyclohexa-2, 5-dienone (V) in methanol and in ether has yielded a photoketone VI and 3, 6-di-*t*-butylguaiacol (VIII) respectively. The irradiation of V in the presence of oxygen in ether has yielded VIII and the hydroperoxide of VI. Other related *p*-quinol ethers have also been subjected to photolysis.

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[19] E. Müller and K. Ley, *Chem. Ber.*, **88**, 601 (1955).