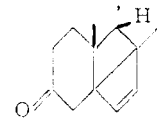
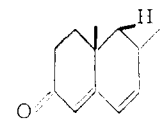
Photoisopyrocalciferol displays bands in the infrared at 970 and 748 cm.$^{-1}$, characteristic of *trans*- and *cis*-symmetrically disubstituted olefins, respectively, and the nuclear magnetic resonance spectrum shows vinyl proton bands at 0 and −1.0 (doublet) p.p.m.[4] The former band is characteristic of the 22-ene structure and thus the latter must be assigned to the remaining nuclear double bond. The large negative displacement is similar to that found for the vinyl proton in cyclobutene (−0.72 p.p.m.).[5] Upon oxidation, the photo compound is converted into a crystalline non-conjugated unsaturated ketone (m.p. 80–81°; C, 85.36; H, 10.62; $\lambda_{max.}$ 1705 cm.$^{-1}$; ϵ_{205} 2350, no. max. at higher wave length) which upon reduction by lithium aluminum hydride is converted to the starting alcohol. Upon ozonization of the acetate, there is obtained a tricarboxylic acid (m.p. 273–275°, C, 64.12; H, 7.51, neut. equiv. 157) which is readily transformed into a cyclic anhydride-carboxylic acid (m.p. 243–244°, C, 66.78; H, 7.62; $\lambda_{max.}$ 1770 and 1825 cm.$^{-1}$). The photo compound can be hydrogenated, stepwise, to yield a dihydro (m.p. 58–59°; C, 84.46; H, 11.58) and a tetrahydro alcohol (m.p. 51.0–52.5°; C, 84.02; H. 12.01); the nuclear double bond is attacked first. All of the foregoing compounds are stable to hydrogen chloride in chloroform solution.[6] These data clearly establish the presence of olefinic linkages at C_6,C_7 and C_{22},C_{23} and they also indicate the presence of a cyclobutene ring and the absence of a cyclopropane structure.

The tetrahydro alcohol upon oxidation with CrO_3 in acetic acid at 0° yields a ketone (m.p. 47.0–48.5°; C, 84.51; H, 11.47; $\lambda_{max.}$ 1705 cm.$^{-1}$; ϵ_{205} 680) whose infrared and ultraviolet spectra are normal for a saturated, isolated ketone. Either the tetrahydro alcohol or ketone upon oxidation with CrO_3 in acetic acid at 70°, followed by esterification with diazomethane, yields a diester (m.p. 65.0–66.5°; C, 77.68; H, 8.47; sapon. equiv., 229), showing the presence of at least one adjacent methylene group. The tetrahydro ketone upon reaction with perbenzoic acid gives rise to a lactone (m.p. 71–73°; C, 81.30; H, 11.31) which when saponified yields a hydroxy acid (m.p. 172–173°; C, 77.59; H, 11.01). Oxidation of the latter compound with CrO_3 in acetic acid at 60° forms the same dibasic acid obtained directly from the ketone, thus indicating the absence of substituents α to the carbonyl group.[7]

When the ketone III derived from the photo compound is allowed to stand with alcoholic alkali, it is converted into oily 4,6-dien-3-one, IV, ($\lambda_{max.}^{EtOH}$ 283 mμ, ϵ 21,00; $\lambda_{max.}$ 1650 cm.$^{-1}$) of the isopyrocalciferol series which can be characterized as a semicarbazone (m.p. 221–223°; C, 77.21; H, 10.12; N, 9.47; $\lambda_{max.}^{EtOH}$ 305 mμ, ϵ 38,500). The same compounds also can be prepared directly from isopyrocalciferol by oxidation followed by base and acid isomerization.



III



IV

Finally, the photo compound II upon heating to 160° in EtOD is reconverted into isopyrocalciferol which is devoid of deuterium. The above facts are only consistent with the valence tautomeric structure II for photoisopyrocalciferol.

Photopyrocalciferol also has been subjected to a similar sequence of reactions and shown to possess an analogous-type structure, different only in the stereochemistry at C_9-C_{10}. This formation of the valence tautomeric structures from 9,10-*syn* structures calls attention to the importance of stereochemistry in the irradiation of 5,7-dienes.

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(4) Parts per million displacement relative to ethanol.

(5) J. D. Roberts and A. T. Bottini, private communication.

(6) D. H. R. Barton, J. E. Page and E. W. Warnhoff, *J. Chem. Soc.*, 2715 (1954).

(7) Preliminary studies of deuterium exchange with the tetrahydro ketone indicate the presence of 4 enolizable hydrogen atoms; the deuterium analyses were kindly performed by Dr. N. R. Trenner, Merck, Sharp and Dohme Laboratories.)

KINETIC ISOTOPE EFFECT IN THE IODINATION OF 2,4,6-TRIDEUTEROPHENOL

Sir:

The bromination of benzene and bromobenzene, and of their tritiated analogs as catalyzed by iodine proceeds without preferential displacement of hydrogen over tritium[1]; likewise bromination of benzene and hexadeuterobenzene by hypobromous acid with an acid catalyst proceeds at identical rates for these two compounds under similar reaction conditions.[2] Similarly no kinetic isotope effect has been found for nitration[1,3] of benzene, toluene, bromobenzene, naphthalene, or nitrobenzene containing tritium or deuterium nor for azo coupling with 1-naphthol-4-sulfonic acid.[4] The conclusion can be drawn that the breaking of the C–H bond has not made much progress in the transition state of the slow step of these electrophilic substitutions and, with less certainty,[5] that an intermediate[6] ArH·E, is formed during this slow step with electrophilic reagent E with loss of the proton occurring in a subsequent fast step.

While the above examples appear to be the only cases in which it has been proven that loss of the proton is kinetically insignificant during electrophilic aromatic substitution, it has been tempting to apply this generalization to other cases. In particular Painter and Soper[7] and Berliner[8] have implicitly or explicitly made this assumption in

(1) L. Melander, *Arkiv Kemi*, **2**, 211 (1950); *Acta Chem. Scand.*, **3**, 95 (1949).

(2) P. B. D. de la Mare, T. M. Dunn and J. T. Harvey, *J. Chem. Soc.*, 923 (1957).

(3) T. G. Boner, F. Bowyer, and G. Williams, *ibid.*, 2650 (1953); W. M. Lauer and W. E. Noland, THIS JOURNAL, **75**, 3689 (1953).

(4) H. Zollinger, *Helv. Chim. Acta*, **38**, 1597, 1617 (1955).

(5) G. S. Hammond, THIS JOURNAL, **77**, 334 (1955).

(6) C. K. Ingold, "Structure and Mechanism in Organic Chemistry," Cornell University Press, Ithaca, N. Y., 1953, p. 279 ff.

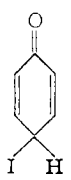
(7) B. S. Painter and F. G. Soper, *J. Chem. Soc.*, 342 (1947); F. G. Soper and G. F. Smith, *ibid.*, 2757 (1927).

(8) E. Berliner, THIS JOURNAL, **73**, 4307 (1951).

their interpretation of the kinetics of the iodination of phenol by solutions of iodine-triiodide ion in water. They concluded that the mechanism of the reaction probably involved attack of I^+ (or H_2OI^+) and acyl hypoiodite (or catalysis of HOI by a general acid HA) upon phenoxide ion. Grovenstein and Henderson[9] have pointed out that the kinetic results available do not exclude a rapid and reversible attack of iodine molecule upon phenoxide ion followed by a slow loss of proton to the solvent or to a general base A^- conjugate to the buffer acid HA.

In order to elucidate further the mechanism of the iodination of phenol, 2,4,6-trideuterophenol was prepared after the general procedure of Ingold[10] and co-workers. After two equilibrations of phenol with heavy water, a product which is estimated to be at least 99% 2,4,6-trideuterophenol was obtained. This phenol undergoes iodination at one fourth the rate of ordinary phenol. Thus in a typical experiment at 25° at initial concentrations of 0.0080 M in phenol and 0.00196 M in iodine, in aqueous solvent which was 0.500 M in acetic acid, 0.050 M in sodium acetate, 0.230 M in sodium perchlorate, and 0.020 M in sodium iodide, the initial apparent second order rate constants (calculated in terms of stoichiometric concentrations of phenol and iodine) were 1.21×10^{-3} l. mole^{-1} sec.$^{-1}$ for ordinary phenol and 3.05×10^{-4} l. mole^{-1} sec.$^{-1}$ for 2,4,6-trideuterophenol. These data give k_H/k_D 3.97. In related runs but in dilute perchloric acid in place of the acetate buffer, isotope effects of similar magnitude were obtained.

The present case, as far as we are aware, constitutes the first example of a hydrogen isotope effect during electrophilic aromatic halogenation. The only other known cases of hydrogen isotope effects during electrophilic aromatic substitution seem to be sulfonation[1,11] (k_H/k_T = 1.8), cyclodehydration[12] of 2-anilino-pent-2-ene-4-one (k_H/k_D = 1.5), and the reactions[4] of some diazonium ions upon hindered 2-naphthol-6,8-disulfonic acid (k_H/k_D = 3.6–6.6). Our present example shows that a phenol need not necessarily be hindered to give an isotope effect. We think it is significant that for the four types of electrophilic substitution reactions for which hydrogen isotope effects are known, three, including the present, involve reactions of phenols or aromatic amines. These are just the types of compounds which would be expected to give the most stable reactive intermediates, thus (I) for iodination of phenol. Substances analogous to (I)



(I)

have indeed been isolated from reactions of 2,4,6-trisubstituted phenols.[13] General evidence, therefore, favors (I) as an intermediate in the iodination of phenol. On this basis, in order to account for both the kinetic evidence and isotope effect, intermediate (I) must, under the kinetic conditions which have been studied,[7,8] be transformed back to reactants considerably faster than into the final products, *i.e.*, (I) must be essentially at equilibrium with the reactants. From such kinetic data, therefore, the nature of the iodinating agent for phenol *cannot be specified.* We hope to be able to find conditions in which intermediates such as (I) from phenols are formed in the rate-determining step; only under such conditions, at best, can the nature of the iodinating agent be ascertained by reaction kinetics. Meanwhile we are investigating the generality of isotope effects during electrophilic halogenation of phenols and related compounds.

(9) E. Grovenstein, Jr., and U. V. Henderson, Jr., THIS JOURNAL, 569 (1956).

(10) C. K. Ingold, C. G. Raisin and C. L. Wilson, *J. Chem. Soc.*, 1637 (1936); A. P. Best and C. L. Wilson, *ibid.*, **28** (1938).

(11) U. Berglund-Larsson and L. Melander, *Arkiv Kemi*, **6**, 219 (1953).

(12) T. G. Bonner and J. M. Wilkins, *J. Chem. Soc.*, 2358 (1955).

(13) Thus see G. M. Coppinger and T. W. Campbell, THIS JOURNAL, **75**, 734 (1953); L. E. Forman and W. C. Sears, *ibid.*, **76**, 4977 (1954); J. A. Price, *ibid.*, **77**, 5436 (1955).

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DETECTION OF FREE RADICAL INTERMEDIATES IN THE ACTION OF OXIDATION INHIBITORS

Sir:

Aromatic amines and phenolic compounds which inhibit oxidation have been presumed to act through the removal of hydrogen from the hydroxyl or amino group:

$$\mathrm{ArXH} + \mathrm{RO_2}\cdot \longrightarrow \mathrm{ArX}\cdot + \mathrm{RO_2H}$$
$$(\mathrm{ArX}\cdot \longrightarrow \text{inactive products}) \qquad k_1 \qquad (1)$$

Recent investigations have brought alternative proposals for the terminating reaction involving these inhibitors. Kooyman and Bickel[1] now suggest two consecutive reactions, both of which terminate oxidation chains

$$\mathrm{ArXH} + \mathrm{RO_2}\cdot \longrightarrow \mathrm{ArX}\cdot + \mathrm{RO_2H}\ k_{1a} \qquad (1a)$$
$$\mathrm{ArX}\cdot + \mathrm{RO_2}\cdot \longrightarrow \text{Stable product}\ k'_{1a} \qquad (1'a)$$

In (1'a) the product is either an adduct or the result of a second hydrogen abstraction.

Boozer, Hammond, *et al.*,[2,3] suggest two consecutive reactions

$$\mathrm{RO_2}\cdot + \mathrm{ArXH} \rightleftharpoons (\mathrm{RO_2ArXH})\cdot K_{1b} \qquad (1b)$$
$$(\mathrm{RO_2ArXH})\cdot + \mathrm{RO_2}\cdot \longrightarrow \text{inactive products},\ k'_{1b} \qquad (1'b)$$

the first of which is reversible and leads to an equilibrium concentration of a radical complex.

Kinetic analysis of the course of an oxidation inhibition period, when the inhibitor acts by the Kooyman and Bickel processes, gives

$$[\mathrm{ArX}\cdot] = \frac{1}{k_0 - 1}[\mathrm{ArXH}]\left\{1 - \left(\frac{[\mathrm{ArXH}]}{[\mathrm{ArXH}]_0}\right)^{k_0 - 1}\right\} \qquad (2)$$

for the concentration of the intermediate radical, where $[\mathrm{ArXH}]_0$ is the concentration of inhibitor

(1) A. F. Bickel and E. C. Kooyman, *J. Chem. Soc.*, 2215–2221 (1956).

(2) C. E. Boozer, G. S. Hammond, C. E. Hamilton and J. N. Sen, THIS JOURNAL, **77**, 3233–3237 (1955).

(3) G. S. Hammond, C. E. Boozer, C. E. Hamilton and J. N. Sen, *ibid.*, **77**, 3238–3243 (1955).