strated that three-membered rings may have different electronic properties as auxochromes.[28] The apparent anomalies may on the one hand reflect the difficulty of interpretation of the perturbations of the complex chromophore systems involved or may reflect real electronic differences in the nature of the rings in these systems.

Experimental Section

Materials.—*cis*- and *trans*-1-cyclohexyl-2-phenyl-3-*p*-phenylbenzoylaziridine were supplied by Dr. N. Cromwell. *cis*- and *trans*-1-cyclohexyl- and -1-benzyl-2,3-dibenzoylaziridine were donated by Dr. H. Heine. *cis*- and *trans*-1-phenyl-2-benzoylcyclopropane, *trans*-1-phenyl-2-*p*-toluylcyclopropane, and 1,1-diphenyl-2-benzoylcyclopropane were donated by Drs. M. Newman and B. Ream. The other compounds were synthesized in this laboratory following procedures described in the literature.

Measurements.—The wavelength maxima and molar absorptivities of each small-ring carbonyl compound in cyclohexane are presented in Table I. The spectra were measured with a Cary recording spectrophotometer, Model 14, using matched 1-cm cells. The maxima were measured by running two or three times over the region of maximal absorption and averaging the values thus obtained. The maxima could be duplicated to at least ±5 A. The molar absorptivities (ϵ) are probably accurate to within ±5%. All measurements were carried out using freshly prepared solutions. The absence of absorbance changes at the maxima for 0.5 hr after the spectrum was recorded was taken as evidence of stability to assure validity of the data. Spectro Grade cyclohexane was used as the solvent in all cases.

Acknowledgment.— The authors wish to thank Dr. N. Cromwell, Dr. H. Heine, Dr. M. Newman, and Mr. B. Ream for supplying compounds used in this investigation. Support of this research by a grant from the National Science Foundation (Grant GP-3972) is acknowledged with appreciation.

(28) L. A. Strait, R. Ketcham, D. Jambotkar, and V. Shah, *J. Am. Chem. Soc.*, **86**, 4628 (1964).

Oxidation Products of Vitamin E and Its Model, 6-Hydroxy-2,2,5,7,8-pentamethylchroman. VIII. Oxidation with Benzoyl Peroxide[1]

W. A. SKINNER AND R. M. PARKHURST

Department of Pharmaceutical Chemistry, Stanford Research Institute, Menlo Park, California

Received October 14, 1965

The reaction of benzoyl peroxide with *dl*-α-tocopherol and its model, 6-hydroxy-2,2,5,7,8-pentamethylchroman, was studied. The major products were confirmed as the 5-benzoyloxymethyl derivatives and, in addition to the previously identified dimers and tocoquinones, trimers were identified as minor products. The decomposition of the 5-benzoyloxymethyl derivative of the model compound was studied under acidic and basic conditions and two new products were identified, compounds XI and XIII. Diels–Alder adducts of the derived quinone methide were also prepared.

In 1955, Inglett and Mattill[2] studied the oxidation of α-tocopherol and its model, 6-hydroxy-2,2,5,7,8-pentamethylchroman, with benzoyl peroxide. The structure proposed for the product from the model was compound I, with the C-7 positional isomer also mentioned as a possibility. When α-tocopherol was allowed to react with benzoyl peroxide, the products were reported to be α-tocoquinone and another compound of unknown structure.

Recently, Goodhue and Risley[3,4] reported on the reaction of *d*-α-tocopherol with benzoyl peroxide in various solvents. They reported that in hexane, benzene, or acetonitrile the product was 5-benzoyloxymethyl-γ-tocopherol (II), which was converted to the dimer III upon treatment with base. By using primary or secondary alcohols as solvents in this reaction products substituted in the 8a position with alkoxy groups (V) were obtained. In *t*-butyl alcohol the major product was dimer III.

We now wish to report on studies we have conducted on the oxidation of *dl*-α-tocopherol and its model, 6-hydroxy-2,2,5,7,8-pentamethylchroman, with benzoyl peroxide and on some interesting chemical transformations of compound I. *dl*-α-Tocopherol was oxidized with benzoyl peroxide at room temperature in benzene, and the benzoic acid produced was precipitated by the addition of petroleum ether rather than by washing with potassium hydroxide, as did Inglett and Mattill,[2] nor was the addition of sodium borohydride used to destroy the excess peroxide, as did Goodhue and Risley.[3]

The results obtained were in general agreement with those of the latter workers. A comparison of the crude reaction products by silica gel thin layer chromatography with the products obtained from the Goodhue and Risley method showed the presence of the same products. Separation of the reaction products by chromatography on a silica gel GF thick plate developed with petroleum ether–benzene (2:1) followed by the isolation of the separated products allowed their identification as trimers[5] A and B, dimer III, 5-benzoyloxymethyl-γ-tocopherol (II), and α-tocoquinone. Treatment of the crude reaction products with base as in the isolation method used by Inglett and Mattill undoubtedly largely converts the 5-benzoyloxymethyl compound to dimer and trimer.[3,5]

We have confirmed that the major product produced upon treatment of the model chroman with benzoyl peroxide in benzene at room temperature is I, as postulated by Inglett and Mattill.[2] Treatment of this product with hydrochloric acid in benzene or with potassium hydroxide in ethanol yielded dimer IV and trimer VI *via* the presumed intermediate quinone methide. The production of these two products

(1) For the preceding papers in this series, see W. A. Skinner and R. M. Parkhurst, *J. Org. Chem.*, **29**, 3601 (1964).

(2) G. E. Inglett and H. A. Mattill, *J. Am. Chem. Soc.*, **77**, 6552 (1955).

(3) C. T. Goodhue and H. A. Risley, *Biochem. Biophys. Res. Commun.*, **17**, 549 (1964).

(4) C. T. Goodhue and H. A. Risley, *Biochemistry*, **4**, 854 (1965).

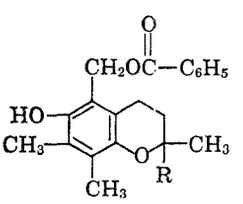
(5) W. A. Skinner and P. Alaupovic, *J. Org. Chem.*, **28**, 2854 (1963).

confirms the position of the benzoyloxymethyl group as being on C-5 rather than C-7.

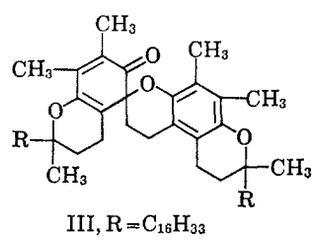
The ease of conversion of I to the *o*-quinone methide prompted us to investigate some reactions of this reactive intermediate. Treatment of I with hydrochloric acid in the presence of dihydropyran afforded the Diels–Alder adduct VII and some trimer VI. Nuclear magnetic resonance allows the assignment of structure VII for the adduct over the alternative one.

Attempts to form adducts from the acid decomposition of I in the presence of maleic anhydride or benzoquinone failed, dimerization and trimerization predominating. In the case of maleic anhydride, the previously obtained[5] maleic anhydride adduct of dimer IV was isolated.

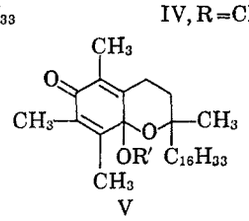
The *o*-quinone methide can also be formed directly from the model chroman *via* oxidation with benzoquinone. When the chroman, benzoquinone, and tetracyanoethylene were refluxed, the adduct VIII was produced.



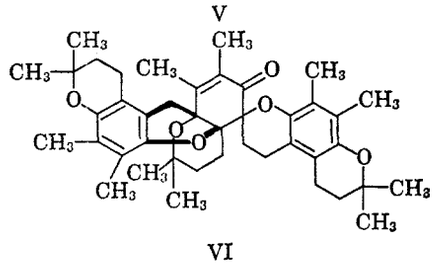
I, R = CH_3
II, R = $C_{16}H_{33}$



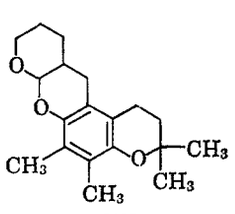
III, R = $C_{16}H_{33}$
IV, R = CH_3



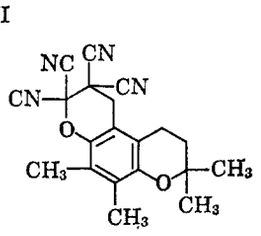
V



VI



VII

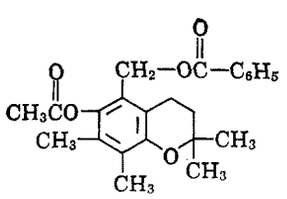


VIII

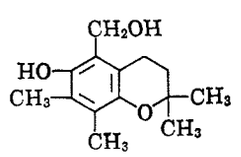
In view of the possibility that the 5-phosphoromethylchroman of vitamin E might have some biological role, it was of interest to attempt to convert the 5-benzoyloxymethyl grouping to the 5-hydroxymethyl derivative as a precursor to this compound. Reduction of I with $LiAlH_4$ in tetrahydrofuran yielded the starting chroman. This is undoubtedly due to the initial formation of the phenoxide ion followed by the leaving of the benzoyloxy group to form the quinone methide, which then yields the chroman under reducing conditions. The synthetic approach of blocking the phenolic hydroxyl by preparation of the acetate IX and its reduction with $LiAlH_4$ also failed. The starting chroman again was obtained.

Treatment of I with hydrochloric acid in ethanol, followed by sublimation of the crude reaction products, gave the aldehyde XI rather than the 5-hydroxymethyl compound. Thin layer chromatography of the crude reaction products on silica gel G indicated the presence of only trace amounts of XI, which indicates that it is formed as a decomposition product during the sublimation. Upon reduction of XI with zinc and acetic acid the starting chroman was obtained. This aldehyde (XI) was also prepared *via* treatment of 6-hydroxy-2,2,7,8-tetramethylchroman with zinc cyanide in the presence of hydrogen chloride, followed by hydrolysis of the intermediate.[6] The identity of the aldehyde produced by sublimation as confirmed by synthesis offers additional confirmation of the C-5 position of the benzoyloxymethyl group in compound I. Attempts to prepare the 6-hydroxy-5-hydroxymethylchroman (X) *via* hydroxymethylation or chloromethylation of 6-hydroxy-2,2,7,8-tetramethylchroman were not successful.

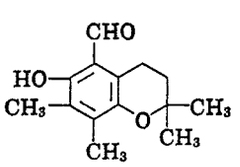
If the products from refluxing the 5-benzoyloxymethyl compound (I) with aqueous hydrochloric acid in ethanol for 3 days under nitrogen were treated with ether–petroleum ether (bp 30–60°) mixtures rather than sublimed, colorless crystals were obtained. Recrystallization of this product from alcohol–water and acetone–water afforded an analytical sample, mp 220°. The infrared spectrum was almost identical with that of the dihydroxy dimer previously reported.[5] The nmr, molecular weight, and elementary analysis were, however, consistent with structure XIII for this compound. This structure requires the elimination of formaldehyde from the 5-benzoyloxymethyl compound and coupling with the 5-methylene group derived from another molecule.



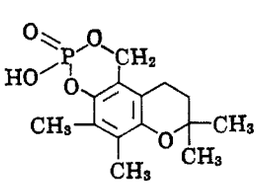
IX



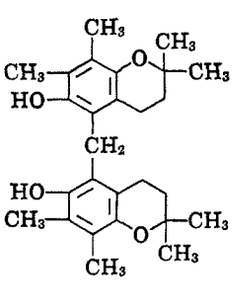
X



XI



XII



XIII

(6) L. Weisler, U. S. Patent 2,592,628 (April 15, 1952).

Attempts to prepare X and the cyclic phosphate XII derived from it are continuing.

Experimental Section

5-Benzoyloxymethyl-γ-tocopherol (II).—*dl*-α-Tocopherol (4 g) in 200 ml of benzene was allowed to react with 3 g of benzoyl peroxide in a similar amount of benzene. After 2 hr at room temperature the solution had changed from pale, olive green to deep yellow, and the benzene was evaporated *in vacuo*. The addition of petroleum ether and cooling allowed most of the benzoic acid to be removed by filtration. The remaining petroleum ether solution was run through a short Florisil (1.5 × 10 cm) column to remove any remaining benzoic acid. Four crude fractions were separated: A, 0.0202 g; B, 1.6583 g; C, 0.4086 g; and D, 0.2667 g. Thin layer chromatography on silica gel GF in benzene showed all fractions to be complex mixtures. Only fraction B (0.5 g) was rechromatographed on a 1-mm thick silica gel GF plate in benzene, and four fractions were eluted. Rechromatography of the two fastest moving materials on similar thick plates gave two materials, each of which appeared as one spot on thin layer in benzene with R_f values of 0.80–0.90 and 0.92–0.96, respectively. The infrared spectrum and thin layer chromatographic behavior of each compound was identical with that of trimers B and A, respectively.[5,7] The third fastest moving material was a yellow compound with R_f (petroleum ether–benzene, 2:1) 0.42–0.48 on silica gel G thin layer and an infrared spectrum that was identical with that of keto ether dimer III. The fourth material was identified as α-tocoquinone from its infrared absorption spectrum and R_f (petroleum ether–benzene, 2:1) of 0.21–0.26.

The purification of 5-benzoyloxymethyl-γ-tocopherol was best accomplished by treatment of the crude reaction product after removal of excess benzoic acid with excess acetic anhydride and pyridine followed by chromatography on Florisil, as reported by Goodhue and Risley.[3] Yields obtained were essentially the same as reported.

5-Benzoyloxymethyl-6-hydroxy-2,2,7,8-pentamethylchroman (I).—This compound was prepared by the same method used in the preparation from *dl*-α-tocopherol except that chromatography was not used because the compound crystallized from ether–petroleum ether mixtures: λ_{max}^{Nujol} (μ) 3.05 (OH), 5.95 (C=O), 6.25 (aryl), 8.60 (C–O–C), and 9.04 (C–O–C, chroman); silica gel G–benzene, R_f 0.21–0.33; chloroform, R_f 0.65–0.73; mp 129–132° (lit.[2] mp 125–126°).

Decomposition of I in Base. Dimer IV and Trimer VI.—Compound I (0.5 g) was dissolved in ethanol and a saturated alcoholic potassium hydroxide solution was added at room temperature. After 1 hr, petroleum ether (bp 30–60°) was added and the layers separated. The petroleum ether layer was washed with water, dried over sodium sulfate, and concentrated *in vacuo*. Chromatography on silica gel G thin layer developed with chloroform indicated that the product was nearly pure dimer IV with small amounts of trimer VI also present.[5]

Decomposition of I with Acid in Benzene. Trimer VI.—Compound I (0.5 g) was refluxed for 5 hr under nitrogen in benzene containing a trace of concentrated hydrochloric acid. Thin layer chromatography on silica gel G developed with chloroform indicated the presence of dimer IV, trimer VI, and hydrolysis products of dimer, as compared with the thin layer behavior of dimer hydrolysis products. Removal of the benzene *in vacuo* and addition of petroleum ether precipitated benzoic acid (79 mg). From the mother liquors was isolated 150 mg of pure trimer VI by elution from a silica gel column with petroleum ether (bp 30–60°).

Decomposition of I with Acid in Ethanol. Compound XI.—Compound I (0.5 g) was refluxed for 12 hr in alcohol containing a trace of concentrated HCl. The thin layer chromatogram of the mixture showed starting material and two other components which moved slower than starting material in the silica gel G–chloroform system used. The solvent was removed from the crude product which was sublimed at 100° (0.5 mm). Bright yellow crystals (80 mg) were obtained. Resublimation removed a more volatile orange impurity in very small amounts. A third sublimation gave an analytical sample melting at 108–110°: λ_{max}^{Nujol} (μ) 6.12 (C=O, aldehyde), 7.67, 7.89, 8.03, 8.55, 8.86, 9.15 (C–O–C, chroman), 10.50, 11.43, and 12.75; absence of OH (3.00) due to hydrogen bonding with C=O. Thin layer chromatography on silica gel G gave R_f values of 0.40–0.46 and 0.74–0.81 using benzene and chloroform as solvents.

Anal. Calcd for $C_{14}H_{18}O_3$: C, 72.03, H, 7.75; mol wt, 234.28. Found: C, 71.85, H, 7.77; mol wt 236.

Synthesis of 5-Formyl-6-hydroxy-2,2,7,8-tetramethylchroman (XI).—A mixture of 6-hydroxy-2,2,7,8-tetramethylchroman (1 g) and 0.5 g of $Zn(CN)_2$ were stirred in dry ether in an atmosphere of dry HCl gas, and over a period of 24 hr three additional 0.5-g portions of $Zn(CN)_2$ were added. The mixture was stirred for several hours after the last addition. A solution of 6 *N* HCl (2 ml) was added, and the ether was evaporated on a water bath. The dark yellow-brown oily product was stirred several hours at steam bath temperatures. The ether extract of this mixture was evaporated and the product chromatographed on silica gel G using chloroform as the developing solvent; yield, 450 mg of yellow crystalline product. The infrared spectrum and thin layer behavior were identical with those of the analytical sample obtained by sublimation of the acid-treated I.

Reduction of XI to 6-Hydroxy-2,2,5,7,8-pentamethylchroman.—Compound XI (2 mg) was treated with zinc dust in dilute acetic acid at boiling temperatures for about 10 min. The colorless product was extracted into benzene and chromatographed on silica gel G thin layer. The product was shown to be model chroman by identity of its infrared spectrum and chromatographic behavior with those of an authentic sample; R_f 0.45–0.55 ($CHCl_3$) and 0.20–0.26 (benzene).

Decomposition of I with Acid–Ethanol (XIII).—Compound I (1 g) in 25 ml of ethanol, 0.5 ml of water, and 0.1 ml of concentrated hydrochloric acid was refluxed for 3 days under nitrogen atmosphere. A thin layer chromatogram indicated a complex mixture of products and the absence of starting material. Evaporation of the solvent and addition of ether–petroleum ether mixtures caused a precipitate of colorless crystals. Recrystallization from alcohol–water and acetone–water mixtures gave 200 mg of a colorless cotton-like crystalline material which melted at 220°. The infrared spectrum looked much like that of the dihydroxy dimer previously reported.[5]

Thin layer chromatography on silica gel G gave R_f values of 0.45–0.51 and 0.12–0.17 using chloroform and benzene as solvents, respectively. The nuclear magnetic resonance spectrum showed a broad peak at τ 5.0 (2 OH) which was destroyed by the addition of D_2O; singlet at 6.15 (CH_2); triplet at 7.27 (2 CH_2); singlet at 7.99 (4 CH_3); triplet at 8.24 (2 CH_2); and singlet at 8.70 (4 CH_3) which was consistent with the methylene bridged dimer structure (XIII) proposed.

Anal. Calcd for $C_{27}H_{36}O_4$: C, 76.4; H, 8.55; mol wt, 424.56. Found: C, 76.8; H, 8.53; mol wt, 402.

6-Acetoxy-5-benzoyloxymethyl-2,2,7,8-tetramethylchroman (IX).—Compound I (1 g) was warmed in excess acetic anhydride–pyridine for 5 hr. The solvent was removed under vacuum and the product crystallized from aqueous alcohol; yield, 1.0 g. An analytical sample was recrystallized from benzene–petroleum ether: mp 105–106°, λ_{max}^{Nujol} (μ) 5.74 (C=O, acetate) and 5.90 (C=O, benzoate).

Thin layer chromatography on silica gel G gave R_f values of 0.13–0.21 and 0.65–0.71 using benzene and chloroform, respectively, as solvents.

Anal. Calcd for $C_{23}H_{26}O_5$: C, 72.35, H, 6.86. Found: C, 72.53, H, 6.96.

Reduction of IX with Lithium Aluminum Hydride.—Compound IX (0.5 g) was refluxed with 0.5 g of lithium aluminum hydride for 3 hr in tetrahydrofuran. Alcohol was added and then saturated sodium sulfate solution. The mixture was filtered and the residue washed several times with ether. Thin layer chromatography, silica gel G–$CHCl_3$, revealed that a complex mixture was formed. The major component was isolated by use of silica gel chromatography ($CHCl_3$) and was shown to be model chroman by its infrared spectrum and thin layer behavior; yield, 100 mg.

Diels–Alder Adducts VII Derived from Quinone Methide.—Compound I (1 g) was refluxed under nitrogen for 48 hr in 30 ml of dihydropyran containing 1 drop of concentrated hydrochloric acid. The solution was evaporated and the product taken up in light petroleum. The petroleum solution was placed on a silica gel column and eluted with petroleum ether–ether mixtures.

(7) W. A. Skinner, R. M. Parkhurst, and P. Alaupovic, *J. Chromatog.*, **13**, 240 (1964).

The first cut was allowed to stand until 120 mg of crystalline trimer was deposited.

The mother liquor was concentrated, and 270 mg of another crystalline product was deposited. Recrystallization from light petroleum ether gave a colorless crystalline product which melted at 117–118°. Thin layer chromatography on silica gel G gave R_f values of 0.23–0.28 in benzene and 0.74–0.81 in $CHCl_3$: λ_{max}^{Nujol} (μ) 6.93, 7.30, 7.35, 8.00, 8.60, 8.75, 8.95, 9.20, 10.04, 10.45, 10.56, 11.32, 11.55, and 11.82; nmr, τ 4.95 (1 H, doublet), 6.35 (2 H, multiplet), 7.55 (4 H, multiplet), 7.9 and 8.0 (two singlets, 4 H and 3 H), 8.1–8.5 (6 H, multiplet), 7.75 (6 H, singlet).

Anal. Calcd for $C_{19}H_{26}O_3$: C, 75.82; H, 8.67; mol wt, 302. Found: C, 75.97; H, 8.77; mol wt, 287.

In another similar run conducted without a nitrogen atmosphere only trimer was isolated.

Diels–Alder Adduct VIII Derived from Quinone Methide.—To 1.08 g of benzoquinone and 1.28 g of tetracyanoethylene in 100 ml of refluxing benzene was added slowly 2.20 g of chroman. After several hours of reflux, the mixture turned a deep purple. After evaporation of the benzene, the solution was chromatographed on a silica gel column with chloroform. The first fraction, a colorless material, was rechromatographed in the same way and sublimed twice: mp 208–210°; yield, 450 mg; λ_{max}^{Nujol} (μ) 4.40 (CN), 6.35, 6.92, 7.10, 8.60, 9.10, 10.30, 10.71, 11.10; nmr, τ 6.30 (singlet, 2 H), 7.40 (triplet, 2 H), 7.75 and 7.80 (singlets, 3 H, methyl), 8.12 (triplet, 2 H), 8.62 (singlet, 6 H).

The Lithium–Liquid Ammonia Reduction of 2-Methyl-2,3-dihydrobenzofuran[1]

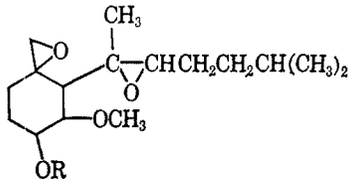
DAVID P. BRUST AND D. STANLEY TARBELL

Department of Chemistry, University of Rochester, Rochester, New York 14627

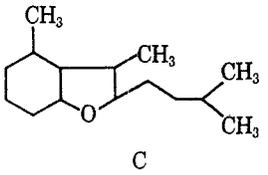
Received July 7, 1965

Reduction of 2-methyl-2,3-dihydrobenzofuran (F) with lithium–liquid ammonia in ether-*t*-butyl alcohol yielded as the main product 2,3,4,7-tetrahydro-2-methylbenzofuran (G) along with some hexahydro-2-methylbenzofuran. Dilute acid hydrolysis gave a mixture of saturated and α,β-unsaturated hydroxy ketones, which was converted to 2-(2-hydroxypropyl)cyclohexanone (K, apparently a mixture of diastereoisomers) by catalytic reduction; the hydroxy ketone was obtained by chromatography on alumina in 16% over-all yield from the dihydrobenzofuran F. The structure of K was established by oxidation to the known α-(2-oxocyclohexyl)-acetone (M) and by unambiguous synthesis from the epoxide of 2-allylcyclohexanone ethylene ketal (N). Thus the lithium–liquid ammonia reduction of 2-methyldihydrobenzofuran yields products analogous to those derived from anisole.

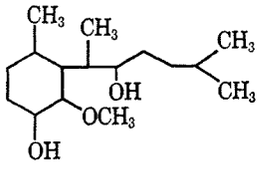
In connection with the synthesis of compounds related to fumagillin[2,3] (A), and particularly of degradation products[2b] such as the alcohol B, the perhydrobenzofuran C, and the monocyclic compound D, we have considered the applicability of the metal–liquid ammonia reduction[4] to phenolic ethers and to 2,3-dihydrobenzofurans.



A, R = CO(CH=CH)$_4$COOH
B, R = H



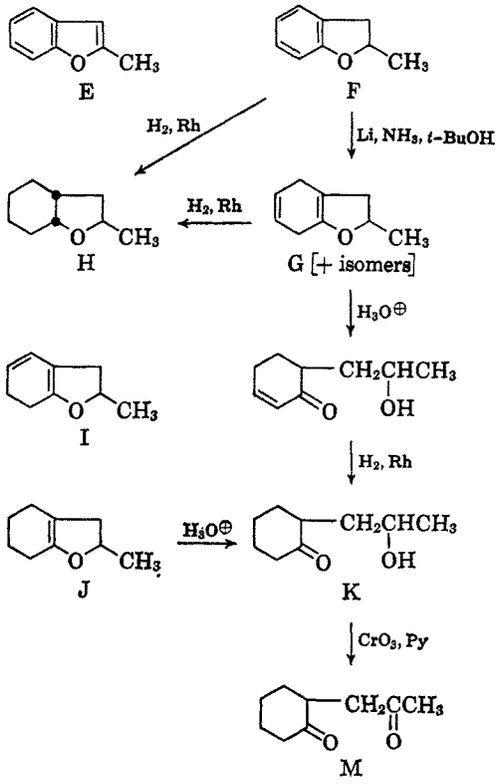
C



D

Hurd[5] showed that an excess of sodium in liquid ammonia reduced 2-methylbenzofuran (E) and the corresponding 2,3-dihydro compound F with ring cleavage to give a good yield of *o*-propylphenol in each case (Scheme I).

SCHEME I



In the present paper, we find that F is converted by the lithium–*t*-butyl alcohol–ether–liquid ammonia pro-

(1) Supported by Grant AI-01138 from the National Institutes of Health.

(2) (a) D. S. Tarbell, *et al.*, *J. Am. Chem. Soc.*, **82**, 1005 (1960); (b) *ibid.*, **83**, 3096 (1961); (c) J. R. Turner and D. S. Tarbell, *Proc. Natl. Acad. Sci. U. S.*, **48**, 733 (1962).

(3) S. T. Young, J. R. Turner, and D. S. Tarbell, *J. Org. Chem.*, **28**, 928 (1963).

(4) For reviews, see (a) A. J. Birch, *Quart. Rev.* (London), **4**, 69 (1950); (b) H. Smith, "Organic Reactions in Liquid Ammonia," Interscience Publishers, Inc., 1963, p 237 ff.

(5) C. D. Hurd and G. L. Oliver, *J. Am. Chem. Soc.*, **81**, 2795 (1959).

(6) (a) A. L. Wilds and N. A. Nelson, *ibid.*, **75**, 5360 (1953); (b) H. L. Dryden, Jr., G. M. Webber, R. R. Burtner, and J. A. Cella, *J. Org. Chem.*, **26**, 3237 (1961).