and evaporated *in vacuo* to give 43.5 mg (84%) of **10**, mp 109–111°.

c. Tetrahydrofuran–Hydrogen Chloride. A solution of **4** (30 mg) in dry tetrahydrofuran (5 ml) was saturated with dry hydrogen chloride for 1 min and the solution was set aside for 1 hr at room temperature under anhydrous conditions. The solvent was removed *in vacuo* and the residual oil crystallized from hexane to give 22 mg (79%) of **10**, mp 108–110°.

d. Sodium Acetate–Methanol. Cyclohexenone **4** (100 mg) was dissolved in methanol (25 ml) containing anhydrous sodium acetate (1 g) and the solution was left at room temperature for 22 hr under nitrogen. The solvent was removed *in vacuo* and the residue was partitioned between ether (100 ml) and water (100 ml). The ether extract was dried ($MgSO_4$) and concentrated *in vacuo* to give an oil. Fractionation on silicic acid (preparative tlc), eluting with ether–hexane (3:1), gave 49 mg (52%) of **10**, mp 109–110°, and recovered **4** (17 mg, 17%).

Methylation of 14a. To cyclohexanedione **14a** (170 mg) in ethanol (5 ml) was added a solution of diazomethane (10 equiv) in ether (40 ml) and the solution was set aside at room temperature for 15 min. The solvent was removed *in vacuo* and the residual oil was fractionated on silicic acid. Elution with ether–hexane (4:1) gave 87 mg (43%) of cyclohexenone **4**, mp 126–128°. Recrystallization from chloroform–hexane raised the melting point to 131–132°. Admixture with an authentic sample gave no depression.

Further elution gave 69 mg (38%) of cyclohexenone **8** as minute crystals, mp 124–126°. Recrystallization from chloroform–hexane raised the melting point to 125.5–126.5: uv (95% ethanol) 250 nm (log ϵ 4.14); ir[25] (KBr) 1726, 1652, and 1610 cm^{-1}; ir[25] ($CHCl_3$) 1720, 1656, and 1615 cm^{-1}; ir[28] (CCl_4) 3490 cm^{-1}; nmr δ 2.80 (broad s, 2, 5-CH_2), 3.63 (s, 3, OCH_3), 3.75 (s, 3, OCH_3), 4.22 (d, 1, J = 1.5 Hz, 1-CH), 4.27 (broad s, exchangeable with D_2O, 6-OH), 5.57 (d, 1, J = 1.5 Hz, 3-CH), 7.4 ppm (m, 5, C_6H_5); mass spectrum[29] (direct insertion) *m/e* 276 (25%, p^+), 157 (38), 128 (51), 125 (24), 105 (100), 77 (35), 69 (21).

Anal. Calcd for $C_{15}H_{16}O_5$: C, 65.21; H, 5.84. Found: C, 65.49; H, 5.93.

Methylation of 14a and b. Triketo ester **2a** (262 mg) in methanol (15 ml) was diluted with 0.2 *M* aqueous sodium bicarbonate solution (15 ml) and the solution was set aside at room temperature for 30 min. The solution was diluted with water (100 ml) and extracted several times with ether to remove most of the methanol. The aqueous layer was acidified with dilute hydrochloric acid to pH 3 and ether extracted, and the ether extracts were immediately treated with diazomethane (10 equiv) in ether (50 ml). The solution was dried ($MgSO_4$) and the solvent was evaporated *in vacuo* to give a pale yellow oil. A portion of the oil was fractionated (preparative tlc) to give **4**, **8**, **9**, and **10** in a molar ratio of *ca.* 2.3:2:1:3.1 (**4** and **10** were isolated as discrete compounds, but **8** and **9** had identical R_f values and were inseparable; the ratio of these was obtained by nmr).

Dehydration of 8. Cyclohexenone **8** (23 mg) was dissolved in dry tetrahydrofuran (5 ml) and hydrogen chloride was passed through the solution for 1 min. After 1 hr at room temperature the solvent was removed *in vacuo*. The residual oil was dissolved in ether, washed with water, dried ($MgSO_4$), and the ether was removed *in vacuo*. The oil crystallized from ether–hexane to give 13 mg (60%) of benzoate ester **12**, mp 140–142°.

(29) Recorded by Mr. C. T. Wetter on an LKB 9000 mass spectrometer.

Ultraviolet Irradiation of α-Apopicropodophyllin

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Abstract: Ultraviolet irradiation isomerizes α-apopicropodophyllin, a 1-phenyltetralin lignan, to a dihydroanthracene derivative. The dihydroanthracene can be dehydrogenated with triphenylmethyl perchlorate to the corresponding anthracene. When tetracyanoethylene is present during irradiation, a diene adduct is formed. The behavior of the ultraviolet absorption spectra during and after irradiation as well as the loss of optical activity is rationalized by postulating an initial photochemical cleavage of α-apopicropodophyllin to a short-lived *o*-quinodimethane intermediate, which can react in several ways.

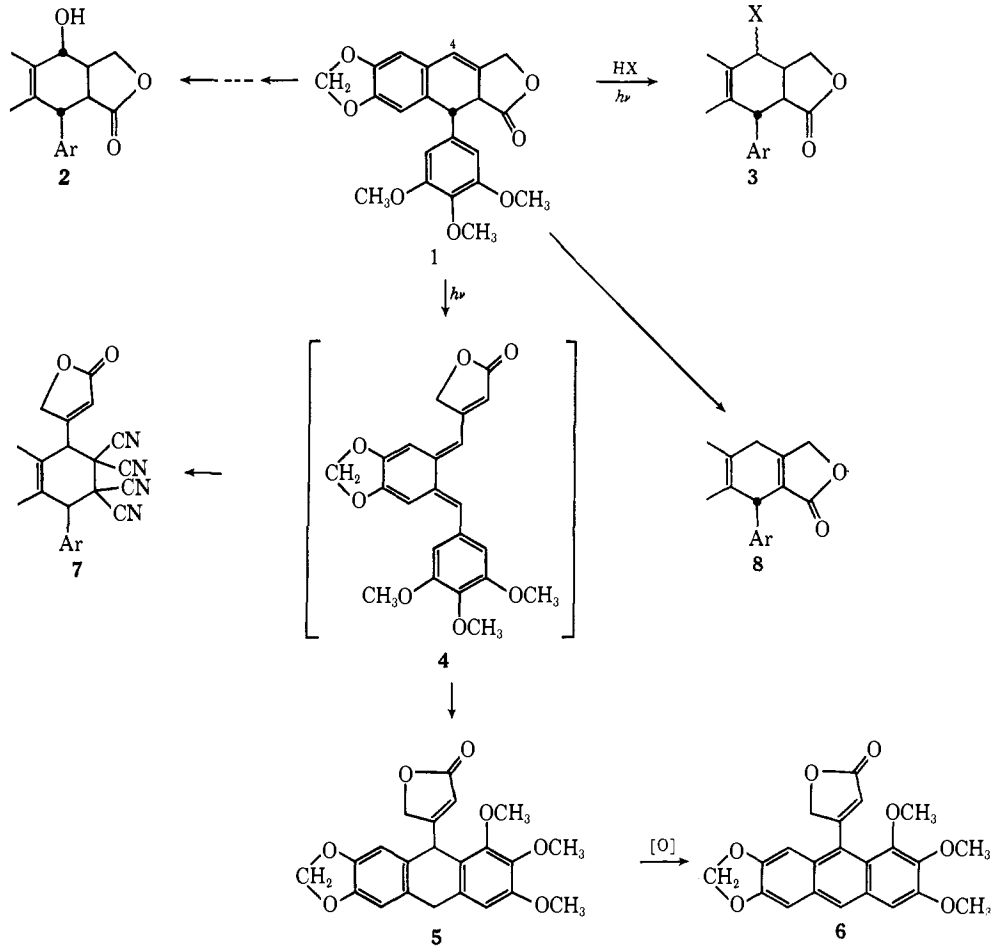
The final stage in a published synthesis of picropodophyllin (**2**) calls for adding the elements of water to the double bond of α-apopicropodophyllin (**1**).[1] The prospect of improving the yields in this conversion[2] led us to try a photochemical process by which ROH is induced to add as RO– and H– to carbon–carbon unsaturation.[3] However, instead of the anticipated reaction giving **3**, an unwelcome ring cleavage intervened. The present report describes our work.

Ultraviolet irradiation of α-apopicropodophyllin (**1**) in slightly acidified aqueous acetic acid transformed the compound to an isomer whose properties are in accord with structure **5**. Thus, disappearance of the characteristic α-apopicropodophyllin absorption maximum at 311 nm in favor of a new 292-nm maximum is consistent

(1) W. J. Gensler, C. M. Samour, Shih Yi Wang, and F. Johnson, *J. Amer. Chem. Soc.*, 82, 1714 (1960).

(2) A closely related hydration gave product in yield no higher than 50%; *cf.* E. Schreier, *Helv. Chim. Acta*, 46, 75 (1963).

(3) Several reports appearing before 1960 first attracted our attention and led to the present work [*cf.* R. Stoermer, *Ber.*, 44, 627 (1911); R. Stoermer and H. Stockmann, *ibid.*, 47, 1786 (1914); but in this connection see P. J. Kropp and H. J. Krauss, *J. Org. Chem.*, 32, 3222 (1967); A. Stoll and W. Schlientz, *Helv. Chim. Acta*, 38, 585 (1955); H. Hellberg, *Acta Chem. Scand.*, 11, 219 (1957); Shih Yi Wang, M. Apicella, and B. R. Stone, *J. Amer. Chem. Soc.*, 78, 4180 (1956)]. More recently many new examples of this kind of photochemically induced addition have been described. In addition to the references included in a survey by J. A. Marshall [*Accounts Chem. Res.*, 2, 33 (1969)] note P. J. Kropp, *J. Amer. Chem. Soc.*, 91, 5783 (1969); P. J. Kropp and H. J. Krauss, *ibid.*, 91, 7466 (1969); T. D. Roberts, L. Ardemagni, and H. Shechter, *ibid.*, 91, 6185 (1969); J. C. Sircar and G. S. Fisher, *J. Org. Chem.*, 34, 404 (1969); J. A. Waters and B. Witkop, *ibid.*, 34, 3774 (1969); A. C. Waiss, Jr., and M. Wiley, *Chem. Commun.*, 512 (1969); W. M. Horspool and P. L. Pauson, *ibid.*, 195 (1967); J. A. Marshall and R. D. Carroll, *J. Amer. Chem. Soc.*, 88, 4092 (1966); C. D. Gutsche and B. A. M. Oude-Alink, *ibid.*, 90, 5855 (1968); P. de Mayo and J. S. Wasson, *Chem. Commun.*, 970 (1967); M. T. McCall and D. G. Whitten, *J. Amer. Chem. Soc.*, 91, 5681 (1969); S. Fujita, T. Nômi, and H. Nozaki, *Tetrahedron Lett.*, 3557 (1969); H. Kato and M. Kawanisi, *ibid.*, 865 (1970).



with the change of **1** → **5**.[4] Also, the intensity behavior of the two carbonyl absorption peaks observed at 1785 and 1750 cm^{-1} for dihydroanthracene **5** matched that noted for simpler β-substituted $\Delta^{\alpha,\beta}$-butenolides. For example, the intensity ratio for the 1785:1750-cm^{-1} peak is less than unity in chloroform but greater than unity in the less polar solvent, carbon tetrachloride.[5] The absence of a ketonic carbonyl in compound **5** was supported by the persistence of these absorption peaks on treatment of the compound with sodium borohydride coupled with their disappearance on treatment with lithium aluminum hydride. Evidence for the presence of an easily oxidizable system was provided by smooth dehydrogenation of the dihydroanthracene **5** with triphenylcarbonium ion[6] to the corresponding anthracene **6**. Interpretation of the fragmentation pattern for compound **5** as well as its nuclear magnetic resonance spectrum on the basis of the assigned formula was both reasonable and structurally significant (see Experimental Section).

Although much noncrystalline material was obtained from the photochemical reaction mixture, no sign of a product corresponding to **3**, where X is acetate, hydroxyl, or chloride, could be detected. Clearly the reaction had taken a course different from the expected addition.

Since β-apopicropodophyllin (**8**) was regularly isolated from the irradiation experiments, we regarded β-apopicropodophyllin at first either as an intermediate in the photochemistry or as a direct end product. However, continued work showed that the β-apopicropodophyllin arose as an artifact, the result of routinely chromatographing the reaction mixture through alumina. Thus, thin-layer chromatography of the crudes showed several spots—including one corresponding to α-apopicropodophyllin—but none for β-apopicropodophyllin; and, in confirmation, when exposure to alumina was avoided, no β-apopicropodophyllin could be isolated. When it was discovered that carrying authentic α-apopicropodophyllin (**1**) through alumina chromatography isomerized it completely to β-apopicropodophyllin (**8**), and that **8** was unaffected by ultraviolet irradiation, we could dimiss the β isomer from any directly pertinent role in the conversions.

The involvement of *o*-quinodimethane **4**[7] as an intermediate was convincingly supported when the irradia-

(4) The closest analog we could locate is 2,3,6,7-tetramethoxy-9,10-dihydroanthracene with an absorption maximum at 295 nm (log ϵ 4.2); A. Müller, M. Raltschewa, and M. Papp, *Chem. Ber.*, **75**, 692 (1942).

(5) R. N. Jones, C. L. Angell, T. Ito, and R. J. D. Smith, *Can. J. Chem.*, **37**, 2007 (1959).

(6) W. Bonthrone and O. H. Reid, *J. Chem. Soc.*, 2773 (1959).

(7) Transient *o*-quinodimethanes are well known, although generally they have been derived by thermal or photochemical processes different from the method used for **9**. Cyclizations analogous to the **4**–**5** conversion as well as diene condensations analogous to the **4**–**7** process also have precedent; *cf.* G. Wittig and M. Leo, *Ber.*, **64**, 2395 (1931); H. Kloosterziel and H. J. Backer, *Recl. Trav. Chim. Pays-Bas*, **71**, 1235 (1952); F. R. Jensen and W. E. Coleman, *J. Amer. Chem. Soc.*, **80**, 6149 (1958); M. P. Cava and A. A. Deana, *ibid.*, 81, 4266 (1959); K. Alder and M. Fremery, *Tetrahedron*, **14**, 190 (1961); K. Sisido, Y. Udô, and H. Nozaki, *J. Org. Chem.*, **26**, 584 (1961); L. A. Carpino, *J. Amer. Chem. Soc.*, **84**, 2196 (1962); M. P. Cava, R. H. Schlessinger, and J. P. Van Meter, *ibid.*, **86**, 3173 (1964); R. Huisgen and H. Seidl, *Tetrahedron Lett.*, 3381 (1964); G. Quinkert, K. Opitz, W.-W. Wiersdorff, and M. Finke, *Justus Liebigs Ann. Chem.*, **693**, 44 (1966).

tion, performed with tetracyanoethylene in the reaction mixture, furnished diene adduct **7** in good yield. Further facts, including the loss of optical activity during irradiation and the observation that the α-apopicropodophyllin 311-nm absorption maximum that was lost on irradiation tended to reappear in a subsequent dark reaction, are brought out in the Discussion below.

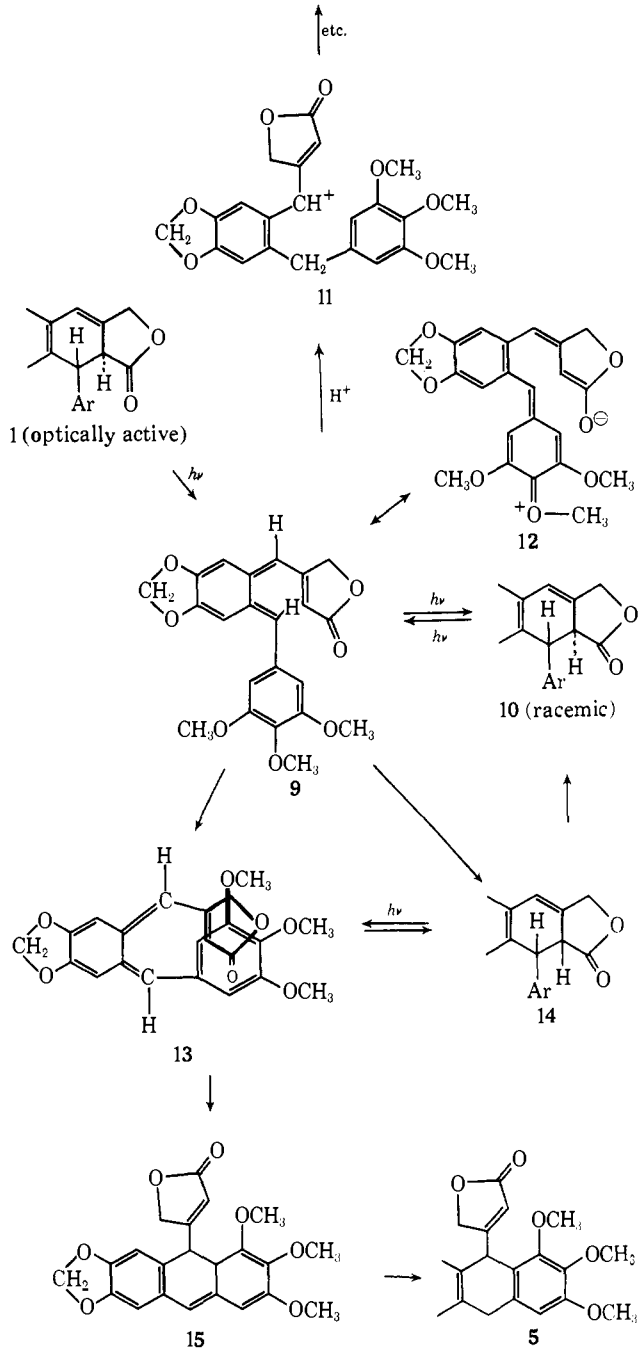
Discussion

Many simple and complex analogies to the **1** → **4** photochemical transformation may be found in the literature.[8] These and in particular a report on the directly relevant parent compound, 1,2-dihydronaphthalene,[9] that appeared after the present work had been completed, made the ring opening postulated here quite reasonable.[10]

If ring opening occurs with conservation of orbital symmetry and therefore in a conrotatory manner,[11] the geometry indicated in **9** may be predicted. Unless nonbonding interactions in the highly crowded molecule prevent coplanarity, contributing form **12** provides a stabilizing factor. Although it is hard to avoid accepting **9** as an early intermediate, the steps after **9** could not be specified in any clear-cut manner. One possible sequence might proceed by the photochemical or thermal cis–trans isomerization, **9** → **13**. Cyclization, again either photochemical[12] or thermal,[13] would give one or the other of the diastereoisomers of dihydroanthracene **15**, which by a prototropic shift[12] would give rise to the product **5**. Another reasonable sequence based on the fact that most of our work made use of a polar solvent (aqueous acetic acid) containing a little hydrochloric acid could start by protonation of the primary photochemical product **9** to give cation **11**, which then would react further by intramolecular electrophilic substitution to lead to the observed product **5**.

Exposure of α-apopicropodophyllin (**1**) to ultraviolet light led to a rapid collapse of the 311-nm maximum and to development of an ultraviolet absorption spectrum resembling that of picropodophyllin (**2**). When the irradiation mixture was stored in the dark and scanned at intervals, the 311-nm maximum was seen to gradually grow back, and the developing spectrum, although never identical, began to approach that of the original α-apopicropodophyllin. The possibility that *o*-quinodimethane **9** was serving as the source of the regenerating α-apopicropodophyllin was eliminated by adding tetracyanoethylene to the solution not before but instead directly after irradiation. This procedure led to no trace of the Diels–Alder product **7**. Since intermediate **4** as a reactive diene would be expected to be rapidly and effectively trapped by condensation with tetracyanoethylene, a potent dienophile, we could conclude that no diene **4** was present and therefore, because it must have only a very short lifetime after the irradiation is interrupted, it could not be the precursor of the re-forming α-apopicropodophyllin.

Compound **14**, the still unknown α-apopodophyllotoxin, suggests itself as an eligible storage form for the regenerating α-apopicropodophyllin. The stereochemistry is consistent with the Woodward–Hoffmann generalizations,[11] since the cis geometry in **14** would be the



(8) References to 1,3-cyclohexadiene–hexatriene interconversions are given by R. O. Kan in "Organic Photochemistry," McGraw-Hill, New York, N. Y., 1966, p 32; P. G. Sammes, *Quart. Rev., Chem. Soc.*, 24, 37 (1970); G. J. Fonken, *Tetrahedron Lett.*, 549 (1962); D. H. R. Barton, *Helv. Chim. Acta*, 42, 2604 (1959). The photochemical cyclization of stilbenes to dihydrophenanthrenes is discussed by D. C. Neckers in "Mechanistic Organic Photochemistry," Reinhold, New York, N. Y., 1967, p 236; see also C. E. Ramey and V. Boekelheide, *J. Amer. Chem. Soc.*, 92, 3681 (1970). Other related systems are described by H. Bach and J. G. Calvert, *ibid.*, 92, 2608 (1970); N. W. Tyer, Jr., and R. S. Becker, *ibid.*, 92, 1289 (1970); K. R. Huffman, M. Burger, W. A. Henderson, Jr., M. Loy, and E. F. Ullman, *J. Org. Chem.*, 34, 2407 (1969); E. F. Ullman, *Accounts Chem. Res.*, 1, 353 (1968); H. G. Heller, D. Auld, and K. Salisbury, *J. Chem. Soc. C*, 682 (1967); B. Weinstein and D. N. Brattesani, *Chem. Ind. (London)*, 1292 (1967).

(9) R. C. Cookson, S. M. de B. Costa, and J. Hudec, *Chem. Commun.*, 1272 (1969).

(10) Interestingly, whereas the photochemistry of substituted 2,4-cyclohexadienones fits the dihydrobenzene–hexatriene pattern, the photochemistry of substituted 1(2*H*)-naphthalenones appears to take a different cause [H. Hart and R. K. Murray, Jr., *J. Org. Chem.*, 35, 1535 (1970)].

(11) R. B. Woodward and R. Hoffmann, "The Conservation of Orbital Symmetry," Academic Press, New York, N. Y., 1970; G. B. Hill, *Quart. Rev., Chem. Soc.*, 22, 338 (1968).

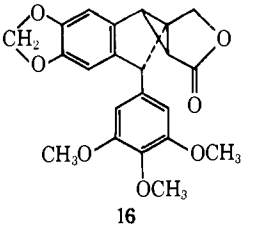
(12) *Cf.* G. Quinkert, W.-W. Wiersdorff, M. Finke, and K. Opitz, *Tetrahedron Lett.*, 2193 (1966).

(13) *Cf.* L. A. Carpino, *J. Org. Chem.*, 34, 461 (1969).

predicted result of a disrotatory thermal cyclization of *o*-quinodimethane (**9**). For α-apopodophyllotoxin (**14**) to be accepted as the storage form, three conditions must be satisfied: first, that **14** form rapidly from **9**; second, that **14** epimerize at a reasonable rate to α-apopicropodophyllin (**10**); and third, that it have little if any absorption at 311 nm. So far as the first proviso is concerned, the transformation of *o*-quinodimethane (**9**) to α-apopodophyllotoxin (**14**), as a symmetry-allowed disrotatory process, may be taken as a relatively facile process. Construction of a molecular model of α-apopodophyllotoxin (**14**) with Dreiding scale models was not possible. Clearly, bond-angle and bond-length distortions as well as nonbonded interactions involving the trimethoxyphenyl group must introduce considerable strain. Although attempts at building a model of α-apopicropodophyllin (**10**) indicate that this molecule too is by no means free of strain, the 1,2 trans configuration in α-apopicropodophyllin provides appreciably more room for the bulky trimethoxyphenyl ring than the 1,2 cis arrangement in α-apopodophyllotoxin. Equilibrium should therefore favor α-apopicropodophyllin, and if the limiting activation energy reflects the energy relation between the two compounds, it is not unreasonable to believe that the **14** → **10** process could be fast enough to accommodate the observations. So far as the ultraviolet absorption is concerned we have little basis for arguing one way or the other on whether the 311-nm maximum, almost surely associated with styrene-like conjugation, should be absent or very weak in α-apopodophyllotoxin (**14**). We hope to prepare and study α-apopodophyllotoxin either to obtain support for our interpretation or to show that it is untenable.[14]

The optical activity in the α-apopicropodophyllin starting material **1** provided another experimental parameter. Monitoring the reaction mixture during irradiation by optical rotatory dispersion measurements showed that the initial activity decreased and finally disappeared. As mentioned before, thin-layer chromatographic analysis of the resulting optically inactive crude product demonstrated the presence of α-apopicropodophyllin (**10**) and dihydroanthracene **5** as well as other materials but not of β-apopicropodophyllin (**8**). Since attempted isolation of α-apopicropodophyllin (**10**) without recourse to column chromatography failed to give a homogeneous product, we resorted to an indirect demonstration. A control experiment showed that the β-apopicropodophyllin (**8**) formed when pure optically active α-apopicropodophyllin is passed over alumina retains all of its optical activity. Accordingly, although alumina effectively catalyzes the prototropic change of α-apo to β-apo, it does not racemize either isomer. When the crude product from the photochemistry was passed over alumina, pure though completely racemic β-apopicropodophyllin could be isolated, a result that proved the presence of racemic α-apopicropodophyllin (**10**) in the optically inactive reaction solution. The absence of optical activity not only in the recovered α-apopicropodophyllin (**10**) but also in diene adduct **7** and in dihydroanthracene **5** is economically accounted for by taking the initial photochemical product **9** either as planar (achiral) or as near planar but with no high barrier to rotation around the single bond connecting the butenolide ring to the rest of the molecule. Thus, loss of optical activity would accompany the very first reaction. The implication that the only optically active material in the mixture is the levorotatory α-apopicropodophyllin starting material itself is borne out by the similarity in appearance of the optical rotatory dispersion curve of the reaction solution taken before irradiation with that taken at an intermediate stage.

Although the above interpretations rationalize our results, other possibilities are not ruled out. For example, a photochemical ring opening of the secondarily formed racemic α-apopodophyllotoxin (**14**) could give rise to *o*-quinodimethane **13**, which could not only cyclize slowly to give intermediate dihydroanthracene **15**, and eventually product **5**, but also cyclize rapidly (disrotatory) to produce α-apopicropodophyllin (**10**). Further, we cannot exclude a photochemical steady state between *o*-quinodimethane (**9**) and α-apopicropodophyllin (**10**) heavily in favor of **9**, or between **13** and **14**. There appears to be no reason for involving a possible intermediate that by analogy with other systems[15]



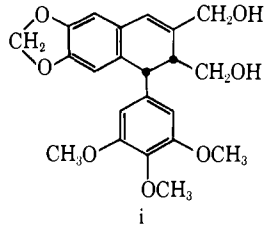
16

would be formulated as **16**.

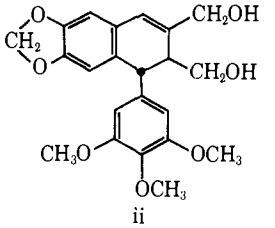
Experimental Section

General. Temperatures are uncorrected. Infrared absorption curves were determined with a double-beam grating spectrophotometer. Ultraviolet absorption curves and optical rotatory dispersion curves were taken with the help of Cary or Beckman recording instruments. A Faraday-effect polarimeter was used for rotations at the sodium D line (589 nm). Most of the nuclear magnetic resonance curves were determined at 60 MHz with chemical shifts reported in parts per million downfield from tetramethylsilane. Analyses for elements were performed by Galbraith Laboratories, Inc., Knoxville, Tenn. Thin-layer chromatography generally made use of commercial silica gel sheets or plates (Gelman; Merck) with spots made visible by exposure to iodine vapor or by fluorescence under ultraviolet. Volatile solvents were removed routinely in a rotary evaporator under water-pump pressures at temperatures no higher than 30–45°. The photochemistry was carried out with an immersion apparatus fitted with a 450-W medium-pressure mercury arc and a water-cooled jacket (Hanovia). Cylin-

(14) Attempts at reaching α-apopodophyllotoxin by a kinetically controlled protonation of the enolate derived from α-apopicropodophyllin so far have not succeeded (unpublished work by John F. X. Judge). α-Apopodophyllol (i) has been reported in one place with uv max 310 and in another place with uv max *ca.* 292 nm (log ε 3.9).



i



ii

The uv max for α-apopicropodophyllol (ii) is close to the latter value. Unfortunately, the absence of a five-membered ring fused on the 2,3 position weakens the comparison with these compounds. [See D. C. Ayres and P. J. S. Pauwels, *J. Chem. Soc.*, 3583 (1965); D. C. Ayres and S. E. Mhasalkar, *ibid.*, 3586 (1965)].

(15) *Inter alia* see ref 9 as well as K. R. Huffman, M. Loy, W. A. Henderson, Jr., and E. F. Ullman, *J. Org. Chem.*, **33**, 3469 (1968).

drical glass sleeves (1-mm wall thickness) were inserted as filters, with wavelength limits for 10% transmission taken as 307 for soft glass, 280 for Pyrex, 250 for Corex, and 212 nm for Vycor.[16] Before turning on the lamp, the reaction solutions were routinely flushed for 0.5 hr with a stream of purified nitrogen. Slow sparging of the magnetically stirred solutions with nitrogen was continued during irradiation. Much of the early work made use of a bank of seven tubular lamps (40-cm Sylvania 15-W Blacklite Blue bulbs) stacked with the long axis horizontal one above the other about 1 cm apart. A fan forced cooling air through holes in the side of the box in which the lamps were mounted and the solutions positioned. This source furnished radiation at 300–400 nm, with the peak output at 350–360 nm.

Starting Materials. Podophyllotoxin (10 g) in 150 ml of absolute alcohol plus 100 ml of 10% aqueous sodium acetate was epimerized by boiling and stirring the solution or 20 hr.[17] After several recrystallizations from absolute alcohol, picropodophyllin (**2**) was obtained in 50–70% yield as cottony needles: mp 229–230°; $[\alpha]_D$ +8° (*c* 0.5, $CHCl_3$); uv max ($CHCl_3$) 290–292 nm; uv max (10^{-4} *M* in 1:1 acetic acid–water) 288 nm (log ϵ 3.57) [lit.[17,18] mp 223.5–224.5°, 226–227°; $[\alpha]_D$ 0, +5.3°; uv max 289 nm (log ϵ 3.66)].

α-Apopicropodophyllin (**1**) wa obtained in 75% yield by dehydrating picropodophyllin (**2**) essentially according to published directions.[19] This α-apopicropodophyllin showed mp 245–246°, $[\alpha]_D$ −15.7° (*c* 0.5, $CHCl_3$),[20] uv max ($CHCl_3$) 311 (log ϵ 3.85) or (1:1 acetic acid–water) 310 (3.88), 299 sh (3.85), 281 sh nm (3.76). Allowing a solution of α-apopicropodophyllin in 1:1 acetic acid–water acidified with a trace of hydrochloric acid to stand in the dark at room temperature produced no change in the ultraviolet absorption curve [lit.[18,19,21] mp variously at 220.5–245°; $[\alpha]_D$ −18°; uv max (95% C_2H_5OH) 311 nm (log ϵ 3.88)]; ir ($CHCl_3$) 1784 and 1593 cm^{-1}; nmr ($CDCl_3$) δ 3.46 (d, 1, J = 3 Hz, H at 4), 3.80 and 3.87 (two s's, 9, $3CH_3O$), 4.21 (d, 1, J = 3 Hz, H at 1), 4.9 (broad s, 2, lactone CH_2O), 5.84 (s, 2, OCH_2O), 6.1–6.92 ppm (complex, 5, H at 4, 5, 7, 2′, 6′).

β-Apopicropodophyllin (**8**) was formed by boiling a solution of α-apopicropodophyllin (0.6 g) in 6 ml of acetic acid containing 0.6 ml of piperidine for 1 hr.[19] After two recrystallizations from chloroform–alcohol, the β-apopicropodophyllin (72%) showed: mp 220–222°; $[\alpha]_D$ +97° (*c* 0.5, $CHCl_3$); uv max (C_2H_5OH) 290 nm or uv max (2 × 10^{-4} *M* in 1:1 acetic acid plus trace of HCl) 291 nm (log ϵ 3.62) with only end absorption at 311 nm (log ϵ *ca.* 2.5) [lit.[1,18,19,21] mp 214–215.4, 216, 220.5–220.9°; $[\alpha]_D$ +100°; uv max 290, 291 (log ϵ 3.7), or (95% C_2H_5OH) 290 nm (log ϵ 3.65)]; ir ($CHCl_3$) 1760, 1690, and 1590 cm^{-1}; nmr ($CDCl_3$) δ 3.58 (s, 1, H at 1), 3.87 (s, 9, $3CH_3O$), 4.15 (s, 2, CH_2 at 4), 4.99 (s, 2, lactone CH_2O), 5.99 (s, 2, OCH_2O), 6.43–6.76 ppm (complex, 4, H's at 5, 8, 2′, 6′). As described below, β-apopicropodophyllin (**8**) could also be obtained by isomerizing α-apopicropodophyllin (**1**) with alumina.

α-Apopicropodophyllic acid, the acid corresponding to α-apopicropodophyllin, was prepared by boiling a solution of α-apopicrodophyllin (0.5 g) in 4 ml of 1:1 aqueous alcohol containing 0.5 g of sodium hydroxide for 20 min.[21] After crystallization from benzene, the α-apopicropodophyllic acid emerged (65% yield) with mp 168–170° dec; $[\alpha]_D$ −163° [lit.[1,19,21] mp 168–169, 173–174°; $[\alpha]_D$ −159.5, −163°; uv max (95% C_2H_5OH) 310.5 (log ϵ 3.86) or 308 nm (3.88)].

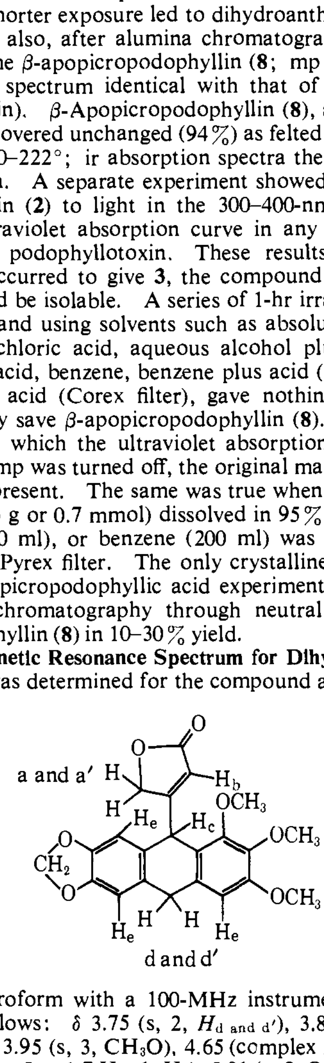
Dihydroanthracene 5 by Irradiation of α-Apopicropodophyllin (1). α-Apopicropodophyllin (0.60 g or 1.5 mmol) was warmed with 160 ml of glacial acetic acid containing 4 drops of concentrated hydrochloric acid until solution was complete. Water (40 ml) was added, and the clear colorless solution was irradiated for 7 hr through a Pyrex sleeve admitting light at wavelengths greater than 280 nm. The resulting yellow solution showed an absorption maximum at 292 but none at 311 nm. The residue left after removing solvent was taken up in benzene and the solution again stripped of volatiles. This was repeated several times. The yellow residual material was chromatographed through a 1.2 × 9 cm column of acid-washed alumina (10 g) with the following eluting solvents collected in 20-ml fractions: benzene (160 ml), 1:1 benzene–ether (40 ml), and 1:1 ether–methanol (20 ml). The solid material (0.12 g) that emerged in benzene fractions 3–7 showed identical infrared absorption spectra and were combined. Since only about 75 mg was found in the other fractions, most of the irradiated material stayed on the column. No β-apopicropodophyllin (**8**) was detected in this run. Two recrystallizations of the solids from ethanol produced glistening colorless or sometimes faintly yellow crystals of dihydroanthracene **5** (20%) with mp 171–172°.

Anal. Calcd for $C_{22}H_{20}O_7$: C, 66.66; H, 5.09; mol wt 396. Found: C, 66.79; H, 5.17; mol wt (osmometric) 401, (mass spectral) 396.

This material produced single spots on silica gel thin-layer chromatography with the following solvents: benzene, benzene–methylene chloride, benzene–methylene chloride–petroleum ether, carbon tetrachloride–ether, and methanol–petroleum ether. No optical activity could be detected either with a polarimeter, $[\alpha]_D$ 0° (*c* 1, $CHCl_3$), or with an optical rotatory dispersion spectrophotometer, $[\alpha]_{500-320}$ 0° (*c* 0.3, $CHCl_3$); uv max (CH_3OH or 95% C_2H_5OH) 292.5 nm (log ϵ 3.78); ir ($CHCl_3$ or CCl_4) 1785 and 1750 cm^{-1}.

When this experiment was repeated using light above 307 nm (soft glass filter), the yield of dihydroanthracene **5** was about the same (22%). Since a control experiment showed that the dihydroanthracene product itself was decomposed slowly by ultraviolet light, a shorter irradiation period of 3 instead of 7 hr was tried. However, the shorter exposure led to dihydroanthracene **5** in lower yield (6%) and also, after alumina chromatography of the crude mixture, to some β-apopicropodophyllin (**8**; mp 215–216°; infrared absorption spectrum identical with that of authentic β-apopicropodophyllin). β-Apopicropodophyllin (**8**), after 7 hr of irradiation, was recovered unchanged (94%) as felted crystals, mp 219–223°; mmp 220–222°; ir absorption spectra the same before and after irradiation. A separate experiment showed that exposure of picropodophyllin (**2**) to light in the 300–400-nm range failed to change the ultraviolet absorption curve in any way. The same was true with podophyllotoxin. These results suggest that if addition had occurred to give **3**, the compound would have survived and would be isolable. A series of 1-hr irradiations through a Pyrex sleeve and using solvents such as absolute alcohol plus a trace of hydrochloric acid, aqueous alcohol plus acid, absolute methanol plus acid, benzene, benzene plus acid (Corex filter), and aqueous acetic acid (Corex filter), gave nothing identifiable on chromatography save β-apopicropodophyllin (**8**). In some of the experiments, in which the ultraviolet absorption was determined just after the lamp was turned off, the original maximum at 311 nm was no longer present. The same was true when α-apopicropodophyllic acid (0.3 g or 0.7 mmol) dissolved in 95% alcohol (200 ml), chloroform (150 ml), or benzene (200 ml) was irradiated for 20 min through a Pyrex filter. The only crystalline materal isolated from the α-apopicropodophyllic acid experiments by a procedure that included chromatography through neutral alumina was β-apopicropodophyllin (**8**) in 10–30% yield.

Nuclear Magnetic Resonance Spectrum for Dihydroanthracene 8. The spectrum was determined for the compound as a 10% solution



in deuteriochloroform with a 100-MHz instrument. The signals appeared as follows: δ 3.75 (s, 2, $H_{d \text{ and } d'}$), 3.80 and 3.90 (two s's, 6, $2CH_3O$), 3.95 (s, 3, CH_3O), 4.65 (complex 2, $H_{a \text{ and } a'}$), 5.16 (s, 1, H_c), 5.37 (q, J = 1.7 Hz, 1, H_b), 5.91 (s, 2, OCH_2O), 6.59 (s, 1, H_e), 6.743, and 6.757 ppm (two s's, 2, $2H_e$). A first-order analysis of this spectrum is consistent with the following spin–spin coupling assignments: $J_{a'b} = J_{ab} \cong J_{bc}$ = 1.6–1.7 Hz; $J_{aa'}$ = 16 Hz;[22] J_{ac} and $J_{a'c}$ = <1 Hz.

(16) J. G. Calvert and J. N. Pitts, Jr., "Photochemistry," Wiley, New York, N. Y., 1967, p 748.

(17) W. Borsche and J. Niemann, *Justus Liebigs Ann. Chem.*, **494**, 126 (1932).

(18) N. L. Drake and E. H. Price, *J. Amer. Chem. Soc.*, **73**, 201 (1951).

(19) A. W. Schrecker and J. L. Hartwell, *ibid.*, **74**, 5676 (1952).

(20) The rotation rises gradually to 0.0° at about 380–390 nm and then more rapidly takes on increasing positive values with decreasing wavelength.

(21) A. Robertson and R. B. Waters, *J. Chem. Soc.*, 83 (1933).

(22) N. S. Bhacca and D. H. Williams ("Applications of NMR Spectroscopy in Organic Chemistry," Holden-Day, San Francisco,

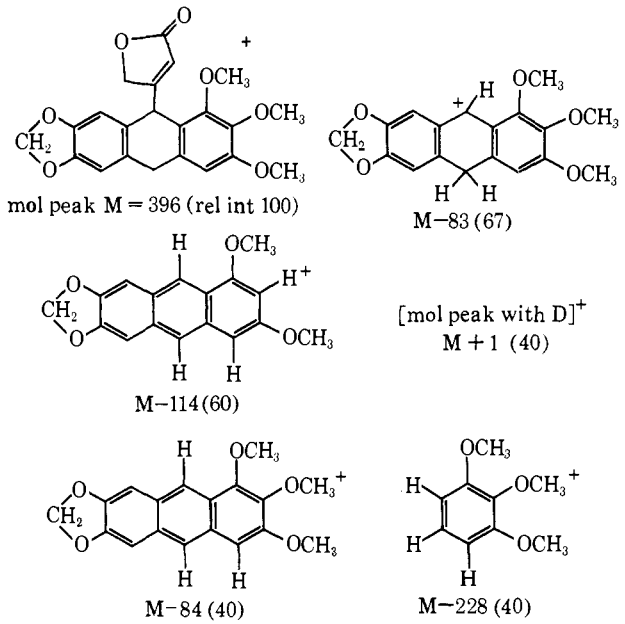
The δ 3.75 signal was seen as a broad singlet, with width at half-height *ca.* 3.5–4 Hz. Decoupling by irradiation at δ 4.65, 5.16, or 5.37 ppm changed the 3.75 signal only very little and indicated minor interactions, if any, between protons d and d′ on the one hand and a, a′, c, and b on the other.

The pattern centered at 4.65 ppm, appearing as an octet of roughly equal intensity peaks about 6 Hz apart accompanied by low-intensity satellites at δ 4.44 and 4.84 ppm, is regarded as the AB part of ABXY, where A and B correspond to a and a′ and X and Y are b and c. When H_b is decoupled by irradiation at 5.37, the pattern changes to a doublet with some sign of further splitting and with the satellite peaks somewhat more prominent; the picture is that of the AB part of ABX, where X is H_c. When the original 4.65-ppm complex is decoupled from H_c by irradiation at δ 5.16, the signals appear as a quartet approximately evenly spaced 5.5 Hz apart and with the satellites more clearly defined. The new quartet is taken as the central cluster of the octet from ABY, where Y = b. Irradiation at δ 3.75 has very little effect on the appearance of the original pattern.

The signal for H_c, a broad singlet ($W_{1/2}$ 3.5–3.8 Hz) at 5.16 suggests weak spin–spin coupling to a, a′, and b and possibly to other protons as well. Decoupling attempts from protons a and a′, b, or d and d′ have very little effect on this signal.

The quartet at 5.37 assigned to H_b corresponds nicely to the pattern expected of X in XA_3. Here the three A protons are all different (a, a′, and c), yet their individual coupling constants with H_b are the same or almost the same. When H_c is decoupled by irradiation at 5.16, the pattern as expected changes to a triplet, the X of an XA_2 pattern with J = 1.6–1.7 Hz. When $H_{a \text{ and } a'}$ are decoupled by irradiation at 4.65, the original quartet at 5.37 becomes a simple doublet, $J_{bc} \cong 1.7$ Hz, corresponding to the X of XA. Irradiation at 3.75 effects little change in the appearance of the H_b signal, so that J_{bd} and $J_{bd'}$ must be very small.

Mass Fragmentation Pattern for Dihydroanthracene 5. The mass spectrum for the dihydroanthracene was determined with the help of a Perkin-Elmer RHV 6 E mass spectrometer at 70 eV and at a volatilization temperature of 200–210°. The prominent peaks listed in the order of decreasing intensities and with suggested structures are as follows. The trimethoxybenzene (M − 228) fragment as a relatively intense peak is also seen in the fragmentation pattern for β-apopicropodophyllin (**8**).[23]



Action of Mixed Metal Hydrides on Dihydroanthracene 5. A solution of dihydroanthracene (40 mg) in 75 ml of ether was treated with excess lithium aluminum hydride (80 mg) and boiled for 5 hr. After adding ice and water, the usual processing afforded 34 mg of white solid that showed new infrared absorption peaks ($CHCl_3$) at 3600 and 3488 cm^{-1} for hydroxyl but that no longer absorbed in the carbonyl region.

In a second experiment, a solution of the dihydroanthracene (20 mg) in 15 ml of absolute alcohol containing 30 mg (excess) of sodium borohydride was stirred at room temperature for 6 hr. After adding glacial acetic acid to destroy unchanged reagent, the mixture was treated in the usual way to recover 18 mg of an oil showing an infrared absorption spectrum ($CHCl_3$) indistinguishable from that of the starting dihydroanthracene **5**. Crystallization from alcohol gave 11 mg of white needles, mp 166–167°; mixed with the starting material, this product showed mp 168°.

Anthracene 6 by Dehydrogenation of Dihydroanthracene 5. A sample of dihydroanthracene **5** (78 mg or 0.20 mmol) was dissolved in 4 ml of warm glacial acetic acid. The solution at room temperature was treated with 75 mg (0.21 mmol) of triphenylmethyl perchlorate[24] and then stirred at 80–90° for 25 min. The mixture, in which the perchlorate had gradually dissolved, was allowed to stand at room temperature for 1 hr. The deposited light brown crystals were collected and washed with a little cold acetic acid and then water before vacuum drying. The filtrate according to thin-layer chromatography contained triphenylmethane. Developed on a thin-layer chromatography place with 4:1 benzene–ethyl acetate, the crystalline anthracene **6** (57 mg or 71%; mp 244–245°) showed a large spot at R_f 0.54 with a minor spot and a little streaking at the base line; no spot corresponding to the starting dihydroanthracene **5** was detected.

About half the crystalline product as a solution in a small volume of chloroform was streaked on a 20 × 20 × 0.2 cm layer of silica gel (Merck) and developed with 4:1 benzene–ethyl acetate. A clearly defined fluorescent strip was scraped from the plate and extracted thoroughly with chloroform. The solvent-free solid isolated from the extract showed mp 244–245°, gave a simple spot on analytical thin-layer chromatography, and corresponded to an 80% recovery. Two crystallizations from glacial acetic acid afforded anthracene **6** as golden yellow flakes (mp 246–248°), which were dried under reduced pressure at 60° for 1 day.

Anal. Calcd for $C_{22}H_{18}O_7$-$(CH_3COOH)_{1/2}$: C, 65.09; H, 4.70. Found: C, 65.26; H, 4.66.

Column chromatography using chloroform as solvent and 200 mesh neutral alumina (Bio-Rad Ag 7) as adsorbent also was satisfactory. The solvent-free material (79% recovery; mp 244–245°) recrystallized three times from acetic acid gave analytically pure product **6**, mp 246–248°.

Anal. Found: C, 65.01; H, 4.76.

Anthracene **6** in chloroform solution showed absorption peaks at 1775 and 1750 cm^{-1}, with relative intensities in line with the generalization advanced for α-unsubstituted $\Delta^{\alpha,\beta}$-butenolides;[5] uv max (10^{-5} *M* for 271 nm; all others 10^{-3} *M* CH_3OH) 392 (log ε 3.81), 369 (3.94), *ca.* 358 sh (3.84), *ca.* 342 sh (3.69), *ca.* 328 sh (3.48), 271 nm (5.03);[25] nmr (CD_3SOCD_3) δ 1.90 (s, 1.5, 0.5 CH_3-COOH), 3.59, 3.82, and 3.89 (three s's, 9, $3CH_3O$), 5.04 (band, 2, CH_2 of lactone), 6.03 (s, 2, OCH_2O), 6.22 (band, 1, olefinic H of lactone), 7.08 (band, 2, 2Ar*H*), 7.18 (s, 1, Ar*H*), and 8.09 ppm (band, 1, Ar*H*). Supporting evidence for the half molecule of solvation was obtained by scanning a deuteriodimethyl sulfoxide solution of acetic acid at roughly the same concentration as from the solvated crystals. As before, the same δ 1.90 ppm peak corresponding to the acetic acid methyl group appeared and no signal for the carboxylic acid proton could be located. The deuterated solvent alone did not absorb at δ 1.90 ppm.

Tetracyanoethylene Adduct 7. α-Apopicropodophyllin (0.60 g; 1.5 mmol) was dissolved in 160 ml of glacial acetic acid containing 4 drops of hydrochloric acid by warming on the steam bath. Tetracyanoethylene (0.19 g; 1.5 mmol) was added at room temperature followed by 40 ml of water. The homogeneous solution was irradiated through a Pyrex sleeve for 7 hr. The reaction mixture was concentrated to a volume of *ca.* 2 ml, and after dilution with 10 ml of 1:1 acetic acid–benzene, was allowed to stand at room temperature. The white felted needlelike crystals were collected, washed with a little 1:1 acetic acid–benzene, and dried. The fact

Calif., 1964, p 45) find J_{gem} = 18 Hz for an analogous methylene group in strophanthidin. Also *cf.* R. G. Coombe, T. R. Watson, and R. M. Carman, *Chem. Ind. (London)*, 1724 (1962); M. E. Wolff and W. Ho, *J. Org. Chem.*, **32**, 1839 (1967).

(23) Mass spectra of compounds related to α-apopicropodophyllin have been determined by A. M. Duffield, *J. Heterocycl. Chem.*, **4**, 16 (1967), and by A. Pelter, *J. Chem. Soc. C*, 74 (1968).

(24) H. J. Dauben, Jr., L. R. Honnen, and K. M. Harmon, *J. Org. Chem.*, **25**, 1442 (1960).

(25) The ultraviolet absorption spectrum compares reasonably well with that reported for 2,3,6,7-tetramethoxy-9,10-dialkylanthracenes by A. Müller, *et al.*;[4] uv max ($CHCl_3$) 393 (log ε 3.6), 377 (3.7), 350 (3.6), 338 sh (3.5), 300 sh (3.5), and 280 nm (4.7). These numbers, taken from the published curves, are approximate.

that the mother liquor was free of even a tinge of yellow pointed to the absence of tetracyanoethylene. The adduct **7** (0.50 g; 61%) was crystallized three times from acetic acid–benzene, but no difference in the melting point was noted before or after recrystallization. The melting behavior, which was markedly dependent on the rate of temperature increase, showed softening at 145–150° followed by frothing at 160–175°.

Anal. Calcd for $C_{28}H_{20}N_4O_7$: C, 64.12; H, 3.82; N, 10.64. Found: C, 64.16; H, 4.13; N, 10.48.

The infrared absorption curve showed peaks at 1790 and 1762 cm^{-1}, with the former more intense in carbon tetrachloride solvent and the latter more intense in chloroform solvent,[5] as well as a sharp, low-intensity maximum at 2273 cm^{-1} (C≡N); uv max (5 × 10^{-4} *M* in CH_3OH) 295 (log ε 3.72), 290 mm (3.71); nmr (CD_3COCD_3) δ 3.75 (s, 9, $3CH_3O$), 5.22 (complex, 3, lactone CH_2 plus either H-1 or H-4 of dihydronaphthalene ring), 5.50 (complex, 1, H-1 or H-4 of dihydronaphthalene), 5.98 (s, 2, OCH_2O), 6.38 (s, 1, Ar–H on methylenedioxybenzene ring), 6.55 (band, 1, olefinic H of lactone ring), and 6.81 ppm (complex, 3, 3 ArH's). The nmr spectra were essentially the same when the solvent was deuteriochloroform instead of deuterioacetone or when the adduct was examined before recrystallizing. Check on the optical rotation showed $[\alpha]_D$ 0.0 (*c* 1, $CHCl_3$); the optical rotatory dispersion from 500 to 320 nm (c 0.3, $CHCl_3$) was uniformly zero.

When this experiment was repeated but with the irradiation time cut from 7 to 1 hr, the yield of adduct **7** was unchanged (64 *vs.* 61%). The infrared absorption curve of the material obtained here was identical with the one obtained from the 7-hr experiment.

A control reaction proved that no adduct **7** formed from α-apopicropodophyllin (**1**) and tetracyanoethylene in the absence of ultraviolet light. A solution of α-apopicropodophyllin (0.3 g; 0.75 mmol) in 50 ml of acetic acid containing 1 drop of concentrated hydrochloric acid plus 97 mg (0.75 mmol) of tetracyanoethylene was diluted with 100 ml of a mixture of acetic acid (160 ml), water (40 ml), and hydrochloric acid (4 drops) that had previously been exposed to ultraviolet through Pyrex for 4 hr. After 7 hr in the dark, this mixture afforded α-apopicropodophyllin (74% recovery) as the only crystalline material. Thin-layer chromatographic analysis (8:2 carbon tetrachloride–ether) revealed no spot corresponding to adduct (R_f 0.51) but did show the presence of tetracyanoethylene (R_f 0.26) and of α-apopicropodophyllin (R_f 0.61).

Another control experiment showed that no adduct formed when the dienophile was added to α-apopicropodophyllin *after* irradiation. Thus, a solution of 0.6 g (1.5 mmol) of α-apopicropodophyllin (**1**) in 160 ml of acetic acid, 40 ml of water, and 4 drops of hydrochloric acid was exposed to ultraviolet light filtered through Pyrex for 1 hr. As soon as the lamp was turned off, tetracyanoethylene (0.19 g; 1.5 mmol) was added, and the solution was allowed to stand away from light for 1.25 hr. This dark brown mixture, concentrated to *ca.* 2 ml and then diluted with 15 ml of 1:1 benzene–acetic acid, failed to deposit crystals. Thin-layer chromatography using carbon tetrachloride–ether (4:1) as developing solvent, showed the presence of α-apopicropodophyllin (R_f 0.5), dihydroanthracene **5** (R_f 0.69), an unidentified material (R_f 0.58), and tetracyanoethylene (R_f 0.22). Thin-layer chromatography with ethyl acetate as solvent showed spots for α-apopicropodophyllin (R_f 0.7), an unidentified material (R_f 0.51), and tetracyanoethylene (R_f 0.13), but no spots for dihydroanthracene **5** nor the tetracyanoethylene adduct **7** (R_f 0.4).

Ultraviolet Absorption of Irradiated Solutions of α-Apopicropodophyllin before and after Standing in the Dark. Table I gives sample readings taken from ultraviolet absorption curves of α-apopicropodophyllin (10^{-4} *M*) that had been dissolved in 1:1 acetic acid–water plus 0.05% hydrochloric acid and exposed to ultraviolet light at 300–400 nm. The measurements, which required no dilutions, were completed generally within 1 min after the indicated irradiation period. After 5 min of irradiations a yellow color developed, and a weak absorption (absorbance *ca.* 0.05) was seen as a tailing at wavelengths on the high side of 380 nm. Reverence to Table I shows that longer exposures lead to decrease in absorption at wavelengths above 310 nm, to little change at *ca.* 295 nm, and to greater absorption at lower wavelengths. The solution obtained after 1 min of irradiation was kept in the dark with aliquots scanned at intervals. Table II gives sample measurements. There is a trend to restore the absorption at 309–311 nm but little tendency to change the situation at 295 nm. The increasing absorption at lower wavelengths, noted with longer irradiation, continues to climb even in the dark and points to involvement of other unspecified reactions. The same general behavior was seen with solutions irradiated for only 0.5 min.

Table I

Irradn time, min	Absorbance (sh or max only where indicated) 319–322 nm	309–311	294–296	266–270
0	0.62 (minor sh)	0.72 (max)	0.68 (sh)	0.40
0.5	0.44 (minor sh)	0.59	0.67 (max)	0.41 (sh)
1	0.26 (sh)	0.49	0.68 (max)	0.43 (sh)
3	0.15 (sh)	0.43	0.68 (max)	0.49 (max)
5	0.22 (sh)	0.46	0.65 (max)	0.68 (max)

Table II

Time after 1-min irradn, min	Absorbance (sh or max only where indicated) 318–323 nm	309–311	294–296	266–270
0	0.26 (sh)	0.50	0.68 (max)	0.43 (sh)
15	0.46 (sh)	0.61	0.66 (max)	0.62 (max)
45	0.57	0.66 (sh)	0.67 (max)	0.71 (max)
105	0.56	0.68 (max)	0.67 (sh)	0.75 (max)

The results from a series of short pilot experiments using 300–400-nm light with 10^{-4} *M* α-apopicropodophyllin in various solvents were consistent with this behavior. Thus irradiation of a solution in acetic acid–water (1:1) containing no hydrochloric acid rapidly eliminated the 311-nm maximum; further, this maximum gradually reappeared when the irradiated solution was allowed to stand in the dark. Similar results were observed with α-apopicropodophyllin in acetic acid–water (4:1) that had been scrupulously freed of oxygen, as well as in diglyme–water (3:1), carbon tetrachloride, or chloroform.

Optically Active β-Apopicropodophyllin (8) from α-Apopicropodophyllin (1) by Alumina Chromatography. A solution of 0.25 g of α-apopicropodophyllin (**1**) in 40 ml of benzene was allowed to flow through a 1.2 × 9.5 cm column of acid-washed alumina (10 g). This was followed by 125 ml of benzene (which eluted little if anything) and then 60 ml of 1:1 benzene–ether. Removal of solvent left 0.19 g of crystals, mp 212–216°, whose infrared absorption spectrum matched that of authentic β-apopicropodophyllin (**8**). Several recrystallizations from absolute ethanol raised the melting point to 217–218°. Thin-layer chromatography (4:1 chloroform–ethyl acetate) produced a single spot (R_f 0.42) running side by side with authentic β-apopicropodophyllin. The optical rotation, $[\alpha]_D$ +104° (*c* 0.5, $CHCl_3$), checked well with the values reported above. Optical rotatory dispersion measurements (c 0.12, $CHCl_3$) showed $[\alpha]_{500}$ +183°; $[\alpha]_{400}$ +383°; $[\alpha]_{340}$ + 633°; $[\alpha]_{335}$ +835°.

Another similar alumina-catalyzed isomerization of α-apopicropodophyllin to β-apopicropodophyllin gave a 93% yield of crystalline product, mp 210–212°, which on a thin-layer chromatography plate (9:1 carbon tetrachloride–ether) developed a single spot (R_f 0.36) matching that of β-apopicropodophyllin but no sign of any spot corresponding to α-apopicropodophyllin (R_f 0.52) on the same plate.

Loss of Optical Activity on Irradiation of α-Apopicropodophyllin (1). A supersaturated solution of α-apopicropodophyllin (0.30 g) in 230 ml of absolute ethanol containing 2 drops of hydrochloric acid showed uv max 311 nm (log ε 3.93). Irradiation through a Pyrex filter for 1 hr changed the initial suspension to a clear yellow solution, with uv max 295 nm. Analysis by thin-layer chromatography (4:1 carbon tetrachloride–ether) revealed spots at R_f 0.61, at 0.56 (α-apopicropodophyllin), and at 0.0 but nothing corresponding to dihydroanthracene **5** (R_f 0.7) or to β-apopicropodophyllin (R_f 0.43). [In another irradiation experiment with the same filter but with acidified aqueous acetic acid as solvent, an aliquot removed after 1 hr and variously diluted for optical rotation dispersion measurements was essentially devoid of optical activity: *i.e.*, $[\alpha]_{350}$ 16 ± 16 or 0 ± 80°; $[\alpha]_{340}$ 33 ± 16, 33 ± 33, or 0 ± 80°; and $[\alpha]_{335}$ 83 ± 33 or 83 ± 83°]. The ethanol solvent was removed and the residue in benzene was chromatographed through a 10-g column of acid-washed alumina. Benzene (200

ml) followed by 1:1 benzene–ether (60 ml) served as the eluting solvent, with 10-ml fractions being collected. The gum (10 mg) emerging with the benzene was discarded. Thin-layer chromatography showed that all the benzene—ether fractions contained β-apopicropodophyllin (R_f 0.4) and that the earlier benzene–ether fractions contained a second material as well (R_f 0.51) which was different from α-apopicropodophyllin. Crystallization of the separate materials from the benzene–ether fractions although giving white fluffy needles did not improve the thin-layer chromatographic picture. The single-spot crystalline β-apopicropodophyllin (**8**) obtained from the later fractions showed mp 215–216° (lit.[1] for racemic β-apopicropodophyllin mp 214–215°), gave an infrared absorption spectrum identical with that from optically active β-apopicropodophyllin, and produced an optical rotatory dispersion curve (*c* 0.3, CH_3OH, or 0.12, $CHCl_3$) devoid of optical activity from 500 to 310 nm.

The decrease in observed rotation on irradiation was consistent with the presence of no optically active material in the reaction mixture other than levorotatory α-apopicropodophyllin. Thus the optical rotatory dispersion curves for α-apopicropodophyllin (*c* 0.3, 4:1 acetic acid–water plus a trace of HCl) had the same shape before and after irradiation for 0.5 hr, and gave the sample readings below.

The 30-min curve taken directly after irradiation was indistinguishable from that obtained after the mixture had been allowed to stand in the dark for several hours. Likewise, the optical rotatory dispersion curve for the α-apopicropodophyllin solution before irradiation was stable for at least this period.

Irradn time,	[α], deg		
min	500 nm	384 nm	350 nm
0	−42 ± 7	0	+306 ± 5
30	−13 ± 6	0	+90 ± 3

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Mechanisms of Hydrolysis of Phosphate Ester Derivatives of Phosphoenolpyruvic Acid

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Abstract: The hydrolytic mechanisms of dibenzylphosphoenolpyruvic acid (I), benzylphenylphosphonoenolpyruvic acid (II), and monobenzylphosphoenolpyruvic acid (III) involve cyclization by the undissociated carboxyl function to expel primarily the thermodynamically unfavorable leaving group, benzyl alcohol (80–90%). Products arising from enolic oxygen–phosphorus bond cleavage comprise the remaining pathway (10–15%). The pH–rate profiles and product studies in aqueous and hydroxylamine solutions suggest pentacovalent phosphorus intermediacy and the rapid, reversible formation of acyclic acyl phosphate or phosphonate in the reactions of I and II. III also forms acyclic acyl phosphate but apparently not reversibly under the experimental conditions. Phosphoenolpyruvic acid also cyclizes to the corresponding five-membered cyclic phosphate under these conditions. Hydrolysis in $H_2{}^{18}O$ indicates that decomposition of the cyclic acyl intermediates occurs with water attack on phosphorus rather than carbon. A rationale is offered for the product composition resulting from hydrolysis and hydroxylaminolysis for I–III and the unusual catalytic efficiency of the carboxyl function.

We have previously investigated the mechanism of hydrolysis of phosphoenolpyruvic acid.[3,4] In an effort to clarify further the effects of protonation and metal ion chelation on the transfer of the phosphoryl moiety from this substrate, we have undertaken a study of di- and monoesterified phosphate ester derivatives of phosphoenolpyruvate. Moreover, these latter systems appear to be examples of neighboring carboxyl group catalysis of phosphate ester hydrolysis. Clark and Kirby[5] originally had observed that either dimethyl- or diphenylphosphoenolpyruvic acid undergoes hydrolysis with loss of methanol or phenol at an accelerated rate relative to trimethyl or triphenyl phosphate at neutral pH. This phenomenon was attributed to intramolecular nucleophilic attack by carboxyl or carboxylate on phosphorus with displacement of alcohol or alkoxide rather than enol or enolate. Recently a similar phenomenon was noted by Blackburn and Brown[6] in the hydrolysis of diethyl-2-carboxyphenylphosphonic acid. A preliminary communication of the results reported here has appeared.[7]

Experimental Section

Materials. Dioxane (purified by distillation over sodium), $H_2{}^{18}O$ (5% BioRad), D_2O (99.8% Diaprep), and twice-distilled, deionized water were employed as solvents. Hydroxylamine hydrochloride (Fisher reagent) was recrystallized prior to use.

(1) Predoctoral Fellow of the National Institutes of Health, 1967–1969. Taken from part of the Ph.D. Thesis of K. J. S.
(2) Career Development Awardee of the National Institutes of Health; Alfred P. Sloan Fellow, 1968–1970.
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