sented above are consistent with this scheme, if k_2 is rate determining for the 2′,6′-dichlorobenzyl compound 1c, but k_1 has become partly rate determining for the propyl compound 1a.

It has been suggested that some biochemical oxidation–reduction reactions, particularly those involving flavins,[12] proceed via covalent adducts of the reactants. The intermediate of Scheme II cannot be covalent, however. Addition of a group to the pyridine ring in 1-d_1 must occur either cis or trans to the deuterium atom; the intermediate is then committed either to transfer of the hydrogen or the deuterium. A mechanism involving addition of the ketone to the dihydropyridine moiety thus requires two separate intermediates, and it can be shown that for such a mechanism, the same relation between kinetic and isotopic partitioning results predicted by Scheme I must hold.

We propose a mechanism involving a common intermediate (or mixture of intermediates) to rationalize the data presented above. We suggest that the intermediate is a noncovalent charge-transfer complex, and that in the first step there is at least some degree of electron transfer from the dihydropyridine to the ketone. The formation of products from the intermediate involves transfer of the hydrogen nucleus and completion of the transfer of electrons, and has a kinetic isotope effect associated with it. The participants in the complex must be capable of some motion relative to one another within a solvent cage, so that either hydrogen may be transferred.[13a] Kosower[13b] has analyzed the energetics of such a one-electron mechanism for reduction of acetaldehyde by a dihydropyridine, and concluded that it is plausible.

Our mechanistic suggestion may be relevant to other dehydrogenase model reactions. Most ordinary ketones are not readily reduced by dihydronicotinamides in the absence of enzymes, and those compounds which are[14] have extensive delocalized π systems with low-lying empty orbitals. It seems likely to us that in all these reactions the electrons are transferred via interaction between the conjugated π systems of the reactants, rather than in close coordination with the hydrogen nucleus. The role that an enzyme plays in making possible reactions between reduced nicotinamide coenzymes and simple carbonyl compounds remains an intriguing puzzle. Spectroscopic evidence suggests that aromatic residues in certain dehydrogenases are capable of strong electronic interactions with the pyridine moiety of bound coenzyme.[15] One can imagine processes in which electronic interaction between coenzyme, substrate, and enzyme allows the separation of electron transfer and proton transfer in these enzymic reactions as well.

(12) G. A. Hamilton and L. E. Brown, J. Amer. Chem. Soc., 92, 7225 (1970).

(13) (a) Ion pairs capable of relative motion without separation have been proposed in other connections; see, for instance, D. J. Cram, "Fundamentals of Carbonion Chemistry," Academic Press, New York, N. Y., 1965, p 98 ff. (b) E. M. Kosower, Progr. Phys. Org. Chem., 3, 81 (1969).

(14) See T. C. Bruice and S. J. Benkovic, "Bioorganic Mechanisms," W. A. Benjamin, New York, N. Y., 1966, p 343 ff.

(15) E. Racker and I. Krimsky, J. Biol. Chem., 198, 731 (1952); C. Cilento and P. Tedeschi, ibid., 236, 907 (1961); S. Shifrin and N. O. Kaplan, Advan. Enzymol., 22, 337 (1960); A. U. Bertland 2nd, Biochemistry, 9, 4649 (1970).

spectral data. We are grateful for research support from the National Institutes of Health (Grant No. AM-12952), and for a grant-in-aid from the Merck Company Foundation.

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The Total Synthesis of Carpanone

Sir:

We described recently a facile, high-yield reaction of o-quinonemethide with nucleophilic olefins such as 1,1-dimethoxyethylene.[1] The total synthesis of carpanone provides an intramolecular example of the utility of this reaction.
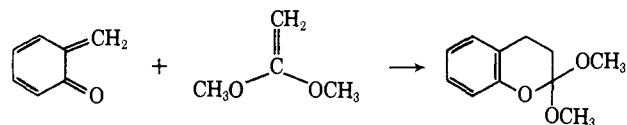
Carpanone (1), a lignan obtained from the bark of the carpano tree,[2] poses a significant synthetic challenge. The molecule possesses no element of symmetry and has five contiguous asymmetric centers. In analyzing the problem, one can imagine the benzodioxane ring to be formed by nucleophilic attack of an enol ether unit on an o-quinonemethide (2). This approach has particular appeal because it may be related to the biosynthesis of carpanone.[2] The required precursor 2 has a C_2 axis of symmetry which passes through the midpoint of the

1   2
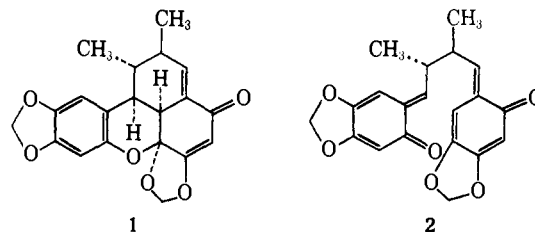
bond joining the two o-quinonemethide units but has neither a center nor a plane of symmetry. Synthesis of a reactive species such as the bis-o-quinonemethide (2) is a formidable task, but Barton's brilliant synthesis of usnic acid[3] suggests that phenolic coupling might succeed. Two problems must be faced in this approach. First, coupling must occur on the styryl double bond rather than the aromatic ring, and, second, the coupling process forms two asymmetric centers which must have the correct stereochemistry. Actually, the stereochemical problem is more difficult than it first appears because the stereochemistry at all centers is determined in the formation of the first bond.

The required 2-(trans-1-propenyl)-4,5-methylenedioxyphenol (3, mp 87–88°) was prepared from 2-allyl-

(1) O. L. Chapman and C. L. McIntosh, Chem. Commun., 383 (1971).

(2) G. C. Brophy, J. Mohandas, M. Slaytor, S. Sternhell, T. R. Watson, and L. A. Wilson, Tetrahedron Lett., 5159 (1969).

(3) D. H. R. Barton, A. M. Deflorin, and O. E. Edwards, J. Amer. Chem. Soc., 78, 530 (1956).
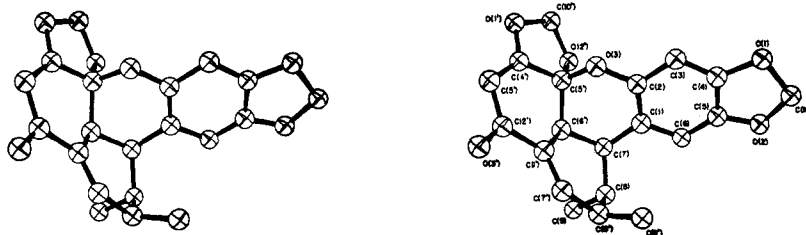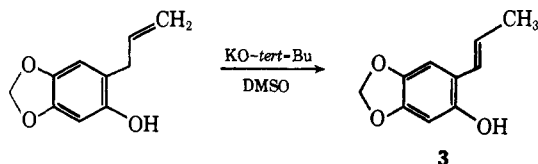
Figure 1. A stereoscopic drawing of the final X-ray model of carpanone less the carbon tetrachloride.

4,5-methylenedioxyphenol[4] by isomerization of the double bond using potassium *tert*-butoxide in dimethyl sulfoxide.

3

Phenolic coupling has been accomplished traditionally by one-electron oxidants, although there is some evidence that two-electron oxidants can be as good or better. In the present case the critical nature of the dimerization step led us to favor oxidation by a divalent metal which could bring two phenolic units together and at the same time effect the required net two-electron oxidation. Palladium(II) was the reagent of choice. Our model of the reaction is shown below.


4   **5 ≡ 1**
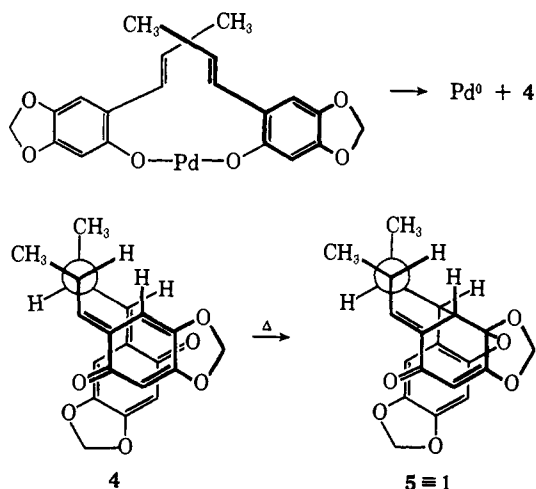
The mode of dimerization shown is the only mode which can give carpanone. The conformation of the double bond at the time of oxidative dimerization must be such that it is oriented away from the phenolic hydroxyl group. If the double bond were oriented toward the hydroxyl group, the o-quinonemethide unit formed would have the wrong stereochemistry.[5] Given the proper conformation of the double bond in both 2-(*trans*-1-propenyl)-4,5-methylenedioxyphenol units, it is still possible to put them together so that the bis-o-

(4) B. H. Alexander, S. I. Gertler, R. T. Brown, T. A. Oda, and M. Beroza, *J. Org. Chem.*, 24, 1504 (1959).
(5) This analysis assumes that rotation about bonds does not occur during oxidation.

quinonemethide has either a C_2 axis of symmetry or a plane of symmetry. Only the bis-o-quinonemethide with C_2 symmetry can give carpanone. In this case the geometry (4) is extremely favorable for nucleophilic attack by the enol ether function of one o-quinonemeth-


wrong stereochemistry

required stereochemistry
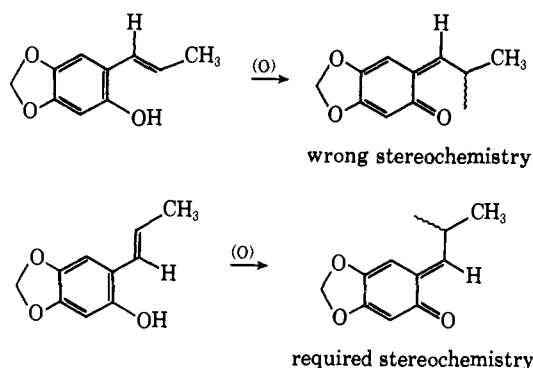
ide unit on the other o-quinonemethide unit to give carpanone (5). Once the carpanone molecule is formed, it equilibrates with a conformer in which the methyl groups occupy pseudoaxial positions. This is the conformation observed in the crystal.

Palladium dichloride (0.8 g) was added to a rapidly stirred (magnetic stirrer) solution containing 2-(*trans*-1-propenyl)-4,5-methylenedioxyphenol (1.6 g) and sodium acetate (6.0 g) in methanol (150 ml) and water (30 ml). The solution was stirred for 2 hr ($\sim$38°) and then left to settle for 1 hr at room temperature. After filtration and dilution with water, the resultant suspension was extracted twice with ether. The ether solution was washed with 10% sodium hydroxide solution and then distilled water. Evaporation after drying over magnesium sulfate gave the crude product (1.0 g, 62%). Carbon tetrachloride (5 ml) was added, and the product crystallized overnight. The crystals (0.98 g, mp 185°) thus obtained contained one molecule of carbon tetrachloride per molecule of carpanone (X-ray crystal structure).[6] Chromatography of the mother liquor gave additional carpanone–CCl₄ (0.08 g). The total yield of crystalline carpanone is 46%. Comparison of the nmr spectra of synthetic and natural carpanone in carbon tetrachloride established their identity.

A single-crystal X-ray analysis was executed to verify the final molecular stereochemistry. Large clear needles were mounted in Lindemann capillaries. Preliminary photographs display 2/m Laue symmetry with systematic absences for $h0l$ ($l = 2n + 1$) and $0k0$ ($k = 2n + 1$). The space group is therefore $P2_1/c$ (C_{2h}^5). A measured density of 1.50 g/cm³ indicated four mole-

(6) The product showed nmr uv spectra identical with those reported for carpanone.[2] The natural product is not optically active.[2]

Communications to the Editor

46%
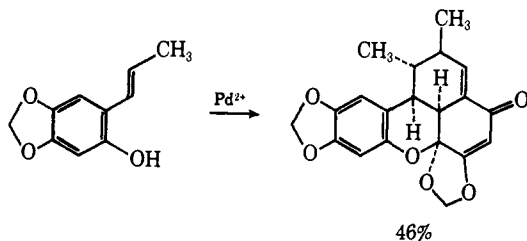
cules of carpanone and four molecules of carbon tetrachloride per unit cell (ρ_{calcd} = 1.51 g/cm³). Diffractometer measured cell constants are a = 19.071 (5), b = 9.721 (5), c = 13.152 (5) Å, and β = 113.11 (5)°. All data in the hkl and $\bar{h}kl$ octants with $2\theta \leq 110°$ were recorded (2647 reflections) with filtered Cu Kα radiation (1.5418 Å). After correction for background, Lorentz, and polarization effects, 1727 reflections were judged observed. A Wilson plot was computed and normalized structure factors were derived in a standard fashion.[7] The 293 largest normalized structure factors were assigned phases by an iterative application of Sayre's equation.[8] All 31 nonhydrogen atoms were revealed in the subsequent E synthesis.[9] Full-matrix least-squares refinements with anisotropic temperature factors for all nonhydrogen atoms and isotropic temperatures factors for all hydrogens are currently at 11.6% for the observed reflections.[10] A computer-generated drawing of the final X-ray model is given in Figure 1.[11] There is no evidence that the carbon tetrachloride is disordered. The closest intermolecular contact is 2.90 Å between chlorine and oxygen. All bond distances and angles in the carpanone molecule agree well with generally accepted values.[12]

The introduction of five contiguous asymmetric centers with the correct stereochemistry in a single high-yield reaction suggests additional uses of palladium(II) in the synthesis of polyphenolic natural products which are now under investigation.

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(8) R. E. Long, Ph.D. Thesis, University of California at Los Angeles, 1965.

(9) J. Rodgers and R. A. Jacobson, "A General Fourier Program in PL1 for Triclinic, Monoclinic and Orthorhombic Space Groups," U. S. Atomic Energy Commission Report IS-2155, Iowa State University, Ames, Iowa.

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(11) C. K. Johnson, "A Fortran Thermal-Ellipsoid Plot Program for Crystal Structure Illustrations," U. S. Atomic Energy Commission Report ORNL-3794, Oak Ridge National Laboratory, Oak Ridge, Tenn., 1965.

(12) "Tables of Interatomic Distances and Configurations in Molecules and Ions," *Chem. Soc. Spec. Publ.*, No. 11 (1958).

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Photolytically Induced Oxygen→Carbon Linkage Isomerization in Formato- and Oxalatoamine Complexes of Cobalt(III)[1]

Sir:

The 254-nm continuous photolysis of $(NH_3)_5CoO_2$-CH^{2+} in $HClO_4$ solution produces Co^{2+}, H_2, and CO_2 with the yields affected by the presence of O_2, 2-propanol, and allyl alcohol; the formation of H atoms and their reaction with the substrate have been established.[2] The flash photolysis of this complex reveals two transients which absorb at $\lambda < 320$ nm, one short-lived (SL) and the other long-lived (LL). Because of the overlap of their spectra, it is not possible to discern whether LL arises from SL or whether they are independent species. However, the spectrum and decay kinetics of LL can be evaluated without any contribution from SL. Point-by-point determination of the absorption spectrum of LL shows a maximum at $\lambda \sim 268$ nm. LL decays *via* first-order kinetics with the rate constant a function of pH as shown in Figure 1a. The activation energy for the decay process is 23 kcal mol⁻¹ independent of pH. The amount of LL and its decay kinetics are independent of the presence of O_2, allyl alcohol, 2-propanol, and (except for the decay rate) H⁺.

The 254-nm continuous photolysis of $(NH_3)_5CoO_2$-CCO_2H^{2+}, $(NH_3)_4Co(C_2O_4)^+$, and $(en)_2Co(C_2O_4)^+$ in $HClO_4$ solution yields Co^{2+}, CO_2, and O_2-scavengeable radicals.[3] The flash photolysis of these complexes, in the presence or absence of O_2, likewise gives two discernible transients which are unaffected by the presence of alcohols or Cl⁻. The pH dependences of the first-order decays of LL are shown in Figures 1a and 1b. The activation energy for these decays has the same value as quoted above within experimental error. The spectrum of LL for $(NH_3)_5CoO_2CCO_2H^{2+}$ is the same as that for $(NH_3)_5CoO_2CH^{2+}$. In 2 M $HClO_4$ the lifetime of LL for $(NH_3)_4Co(C_2O_4)^+$ is sufficiently long for a spectrum to be obtained by double beam spectrophotometry within 1 min of the flash. An absorption maximum at $\lambda \sim 265$ nm is observed; the parent complex does not have an absorption maximum in that region. Intermediate LL for $(en)_2Co(C_2O_4)^+$ (en-LL) is so long lived[4] in highly acidic medium that it can be generated by continuous photolysis and separated from Co^{2+} and the substrate by ion-exchange chromatography.[5] Although we have been unable to isolate en-LL as a solid,[6] its spectrum in acidic solution has been characterized and is shown in Figure 2 in comparison with $(en)_2Co(C_2O_4)^+$. Intermediate en-LL decays quantitatively to Co^{2+} with a first-order rate constant identical with that seen from flash photolysis; CO_2 is also produced in this reaction. Intermediate en-LL undergoes base-catalyzed hydrolysis to yield $(en)_2Co(OH_2)_2^{3+}$.

The following facts are evident from the data: (1) the LL intermediate from the formato and monodentate