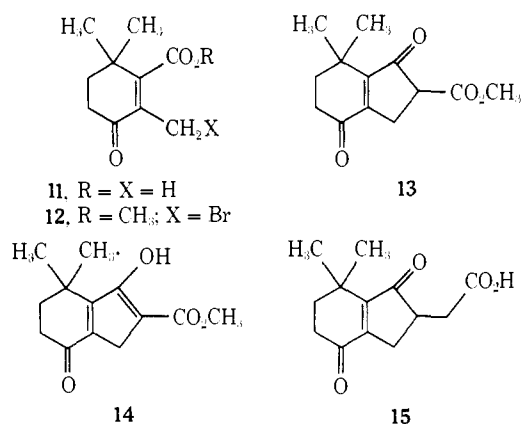


vinyl proton of the alkoxyethylene lactone (nmr (CDCl_3) δ 7.37 (1, d, $J = 2.4$ Hz) vs. 7.42 (1, d, $J = 2.5$ Hz) for strigol) indicating that the desired *E* isomer was selectively formed.

With this assurance in hand, we then proceeded with the synthesis of the hydroxylactone **3**. 2,6,6-Trimethylcyclohex-1-en-3-one-1-carboxylic acid (**11**)¹¹ was esterified (CH_3I , acetone, K_2CO_3 , 25° , 12 hr) and then treated with *N*-bromosuccinimide in CCl_4 to give the bromide **12**¹⁰ in nearly quantitative yield. Reaction of **12** with excess dimethyl sodiomalonate in methanol resulted in alkylation and cyclization to give a mixture of the β -keto ester **13** and its enol **14**¹⁰ (80% overall yield from **11**). Alkylation of this mixture with methyl bromoacetate (K_2CO_3 , THF, 25° , 48 hr) followed by acidic hydrolysis (acetic acid-6 *N* HCl, 1:1, reflux, 3 hr) gave diketo acid **15**: mp 136.5 – 137° (benzene);



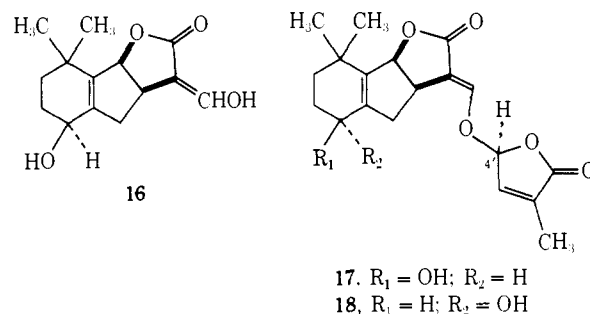
uv_{max} (95% $\text{C}_2\text{H}_5\text{OH}$) 260 nm (ϵ 13,300); ir (KBr) 3350–2500 (acid OH), 1710 ($\text{C}=\text{O}$ and acid $\text{C}=\text{O}$), 1682 cm^{-1} ($\text{C}=\text{O}$); nmr (CDCl_3) δ 1.33 (3, s), 1.95 (2, m), 2.35–2.88 (7, complex), 10.7 (1, br); (70%).

Reduction of **15** with diisobutylaluminum hydride (4 equiv) in CH_2Cl_2 (-70° , 3 hr) afforded a mixture of hydroxylactones **3** and **4** (60% yield) in a ratio of ca. 2:1. Separation of the two isomers was achieved by preparative thin-layer chromatography (silica gel, CHCl_3 -acetone, 95:5, ten developments) yielding the slower moving component at the desired isomer **3**: mp 143 – 144° (benzene-hexane); nmr (CDCl_3) δ 1.08 (3, s), 1.14 (3, s), 1.4–3.0 (9, complex), 4.12 (1, t, $J \approx 5$ Hz), 5.48 (1, d, $J = 6.8$ Hz); ir (CHCl_3) 3600 and 3480 (OH), 1764 cm^{-1} (lactone $\text{C}=\text{O}$). Elution of the faster moving component yielded the diastereomeric hydroxylactone **4** as an oil: nmr (CDCl_3) δ 1.09 (3, s), 1.13 (3, s), 1.4–3.0 (9, complex), 4.18 (1, t, $J = 4.9$ Hz), 5.49 (1, d, $J = 5.4$ Hz); ir (CHCl_3) 3600 and 3480 (OH), 1760 cm^{-1} (lactone $\text{C}=\text{O}$).

Hydroxylactone **3** was condensed with methyl formate (NaH, ether, 25° , 20 hr), and the resulting hydroxymethylene lactone **16**¹⁰ (78% yield) was alkylated with bromobutenolide **9** (K_2CO_3 , HMPA, 25° , 12 hr) to give a mixture of *dl*-strigol (**1**) and *dl*-4'-epistrigol (**17**).¹²

(11) Prepared from citral by a modification of the route of G. Wendt, *Chem. Ber.*, **74**, 1242 (1941). More direct routes to **11** are currently under study.

(12) Similar transformations starting with the epimeric hydroxylactone **4** led to two other isomers of strigol (isomers C and D; **2** and **18**) possessing the unnatural configuration of the C-4 hydroxyl. These isomers were clearly distinguishable from those in the natural series by nmr spectroscopy although the ir spectra in CH_2Cl_2 were nearly identical for all four isomers.



This mixture was cleanly separated by preparative thin-layer chromatography (silica gel; CHCl_3 -acetone, 4:1) to give isomer A ($R_f = 0.32$, mp 178 – 180° (ethyl acetate-hexane), ca. 25% yield) and isomer B ($R_f = 0.20$, mp 203 – 205° dec (ethyl acetate-hexane), ca. 25% yield). As the ir, nmr, uv, and mass spectra of both isomers A and B (**17** and **1**) are essentially identical with those of natural strigol, the relative biological potencies of these two isomers are currently being examined to ascertain the configuration at C-4'.¹³

Acknowledgment. We wish to thank Dr. C. E. Cook for helpful communications. Partial support of this work by the National Institutes of Health (AM-04874) and the Wisconsin Alumni Research Foundation is gratefully acknowledged.

(13) NOTE ADDED IN PROOF. Isomer B was found to be chromatographically identical with a sample of strigol kindly provided by Dr. Cook. Concentrations required for the 50% germination of striga seeds were 10^{-12} M for isomer A and 10^{-16} M for isomer B. We thank Dr. D. E. Moreland for these biological data.

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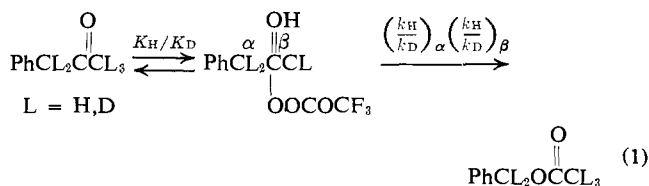
School of Pharmacy, University of Wisconsin
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Received January 14, 1974

Secondary Deuterium Isotope Effects in the Baeyer-Villiger Reaction

Sir:

The application of secondary deuterium isotope studies to chemical reactions is a powerful technique for garnering mechanistic insights.¹ When the reaction mechanism can be established independently, more subtle inferences about the transition state may be made.¹ The Baeyer-Villiger reaction has been shown to follow the mechanism given below, migration being



synchronous with the departure of the leaving group.^{2,3} We report observed isotope effects for the Baeyer-Villiger reaction of $\text{PhCD}_2\text{COCH}_3$ (D_2), $\text{PhCH}_2\text{COCD}_3$

(1) For reviews see S. E. Scheppelle, *Chem. Rev.*, **72**, 511 (1972); C. J. Collins and N. S. Bowman, Ed., "Isotope Effects in Chemical Reactions," Van Nostrand Reinhold, New York, N. Y., 1970; E. R. Thornton, *Annu. Rev. Phys. Chem.*, **17**, 349 (1966); E. A. Halevi, *Prog. Phys. Org. Chem.*, **1**, 109 (1966); L. Melander, "Isotope Effects on Reaction Rates," Ronald Press, New York, N. Y., 1960.

(2) (a) M. F. Hawthorn and W. D. Emmons, *J. Amer. Chem. Soc.*, **80**, 6393, 6398 (1958); (b) B. W. Palmer and A. Fry, *ibid.*, **92**, 2580 (1970).

(3) M. A. Winnik and V. Stoute, *Can. J. Chem.*, **51**, 2788 (1973).

Table I. Kinetic Isotope Effects for the Baeyer–Villiger Reaction and Equilibrium Isotope Effects for Hemiketal Formation from Phenyl-2-propanone

Ketone	% isotopic purity ^a	$(k_H/k_D)_{\text{obsd}}^b$	No. of experiments	K_H/K_D^c	No. of experiments ^d
PhCD ₂ COCH ₃	87.3	0.932 ± 0.004	7, 6 ^f	0.87 ± 0.03	2
PhCH ₂ COCD ₃	88.5	0.921 ± 0.006	2, 2	0.79 ± 0.07 ^g	
PhCD ₂ COCD ₃	87.0	0.858 ± 0.006	7, 6	0.68 ± 0.04	3

^a At completion of the studies. Deuterium content decreased about 3% per year. ^b Observed kinetic isotope effects in methylene chloride at 22 ± 1°. Mean value for the number of experiments indicated in the next column. Errors are standard deviations. For each experiment, 30–40 values of the parent ion intensity ratios at 70 eV were averaged with an error of 0.6%. ^c Methyl hemiketal formation in 3 M methanol–dioxane. ^d Each experiment represents simultaneous examination of the deuterated and nondeuterated ketone at seven different concentrations for each. ^e 2–15% conversion. ^f 100% reaction. ^g Calculated from $(K_H/K_D)_{D_2}(K_H/K_D)_{D_3} = (K_H/K_D)_{D_5}$.

(D₃), and PhCD₂COCD₃ (D₅). Modeling the pre-equilibrium step, we measured K_H/K_D for hemiketal formation. We show how these values can be manipulated to yield the α and β isotope effects for the migration step. The β isotope effect indicates that, in the transition state for migration, considerable carbon–oxygen double bond formation has occurred, implying a later transition state in the Baeyer–Villiger reaction than in the mechanistically similar pinacol rearrangement.⁴

Phenyl-2-propanone is easily exchanged to give D₅. Syntheses of D₂ and D₃ have failed in the past.⁵ We were fortunate enough to find conditions for selective exchange in pyridine, reported elsewhere,⁶ which yielded them in high yield and isotopic purity (see Table I). These ketones are extremely sensitive to exchange. Oxidation with CF₃CO₃H was carried out in methylene chloride at 22 ± 1° in the presence of a twofold excess of scrupulously dry Na₂HPO₄.⁷ Aqueous solutions used in the work-up were buffered at pH 6.5. Mass spectrometric analyses were carried out within 4 days of the reaction. Reactions run to low conversion were compared to those run to completion. In spite of precautions, the isotopic purity of the ketones changed noticeably over 1 month.

We used eq 2, a modification of Collins' competition method,⁸ to obtain values of the isotope effects independent of the isotopic purity of the ketones. Assuming that no exchange takes place during the reaction,⁹ the mass spectrometric ion ratios, m/e 150/152, 150/153, and 150/155, for 100% reaction are proportional to the mole ratios of isotopically pure ketones in the reactants. If these ion ratios are normalized to equal moles of D_L ($L = 2, 3, 5$) and D_0 , they may be compared to the normalized ion ratios for reaction to low conversion. These are respectively the denominator and numerator in eq 2. The values obtained from eq 2 are independent of isotope effects in the mass spectrometer and of the

$$\left(\frac{k_H}{k_D}\right)_{\text{obsd}, D_L} = \lim_{1c \rightarrow 0} \frac{m/e(150/Y)_{1c}}{m/e(150/Y)_{100\%}} \quad (Y = 152, 153, 155) \quad (2)$$

specific isotopic purity of the deuterated ketones. The results are presented in Table I.

An important check on the consistency of our results follows from the necessity that PhCD₂ and CD₃ make the same contribution to the isotope effect in D₅ as in the respective D₂ and D₃ ketones. Thus $(k_H/k_D)_{\text{obsd}, D_2} \cdot (k_H/k_D)_{\text{obsd}, D_3} = (k_H/k_D)_{\text{obsd}, D_5}$. The product of 0.932 × 0.921 = 0.858, which compares better than one might expect to the measured value of 0.858 for D₅.

While the observed isotope effects are consistent either with rate-determining addition^{10, 11} to the carbonyl or rate-determining migration, rate-determining addition in the Baeyer–Villiger reaction is known only for aromatic ketones and aldehydes substituted with electron donating groups.^{2b, 12} For phenyl-2-propanone, rate-determining migration is indicated since aliphatic ketones undergo faster addition and slower migration than aromatic ketones, which, under conditions similar to ours, are known to suffer rate-determining migration.² Accordingly, the observed isotope effects must be interpreted in terms of an equilibrium isotope effect for formation of the tetrahedral intermediate in combination with a kinetic isotope effect for the rate-determining migration.

Three equations may be derived from the Criegee mechanism assuming slow migration and low concentrations of the adduct.¹³

$$(k_H/k_D)_{\text{obsd}, D_2} = (K_H/K_D)_{D_2} k_\alpha^2 \quad (3)$$

$$(k_H/k_D)_{\text{obsd}, D_3} = (K_B/K_D)_{D_3} k_\beta^3 \quad (4)$$

$$(k_H/k_D)_{\text{obsd}, D_5} = (K_H/K_D)_{D_5} k_\alpha^2 k_\beta^3 \quad (5)$$

(4) W. M. Schubert and P. H. LeFevre, *J. Amer. Chem. Soc.*, **94**, 1639 (1972); **91**, 7746 (1969).

(5) P. Geneste, G. Lamaty and J. P. Roque, *Tetrahedron*, **27**, 5539 (1971).

(6) M. A. Winnik, *Synthetic Commun.*, **3**, 279 (1973). This paper contains not only the synthetic experimental details but complete information on the isotopic purity of ketones used in this study.

(7) Under these conditions, methyl migration occurs to less than 0.02%.³ At 100% conversion the yield of benzylacetate (glc and nmr) was 95–97%. Some benzyl trifluoroacetate formed (3–5%). The effect of ester exchange was neglected in calculating the observed isotope effects.

(8) C. J. Collins, *Advan. Phys. Org. Chem.*, **2**, 1 (1964).

(9) No exchange was observed by nmr; 1% could have been detected. The ketones underwent extensive exchange in the mass spectrometer, although the product esters were stable and showed identical isotopic composition with those of the ketones measured by nmr.

(10) (a) J. M. Jones and M. L. Bender, *J. Amer. Chem. Soc.*, **82**, 6322 (1960); (b) M. L. Bender and M. S. Feng, *ibid.*, **82**, 6318 (1960); (c) V. F. Raaen, T. K. Dunham, D. D. Thompson, and C. J. Collins, *ibid.*, **85**, 3497 (1963); (d) M. Cherest, H. Felkin, and C. Frajerman, *Tetrahedron Lett.*, 379 (1971).

(11) Rate-determining ketone protonation should have $(k_H/k_D)_{\text{obsd}} > 1$, since protonating the oxygen increases the amount of positive charge on the carbonyl carbon.¹ $K_H/K_D = 1.29$ for protonation of acetophenone and its CD₃ analog: E. M. Arnett, T. Cohen, A. A. Bothner-By, and R. D. Bushick, *Chem. Ind. (London)*, 473 (1961).

(12) Y. Ogata and Y. Sawaki, *J. Amer. Chem. Soc.*, **94**, 4189 (1972).

(13) Secondary isotope effects for carbonyl addition equilibria are primarily sensitive to ketone structure.⁵ Limited evidence suggests that other factors such as carbon–nucleophile bond distance in the adduct and solvent are of lesser importance. Although the quantitative values we calculate for k_α and k_β depend upon a model for the pre-equilibrium step, our conclusions are not very sensitive to this assumption.

Here k_α is the isotope effect per deuterium for PhCD_2 migration where CH_3 is the nonmigrating group; k_β is that for PhCH_2 migration where CD_3 is the nonmigrating group. K_H/K_D refers to the respective equilibrium isotope effects for addition to the carbonyl. In order to obtain values for the α and β isotope effects, we must measure or simulate values for K_H/K_D .

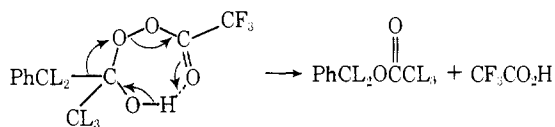
Jones and Bender^{10a} measured the isotope effect for methyl hemiketal formation for acetone in methanol-dioxane and for cyclopentanone in methanol. We applied their method to phenyl-2-propanone in 3 M methanol in dioxane. We measure $(K_H/K_D)_{\text{D}_2} = 0.87 \pm 0.03$ and $(K_H/K_D)_{\text{D}_5} = 0.68 \pm 0.04$. These may be compared to Bender's measurements^{10a} of 0.78 for acetone- d_6 and 0.69 for cyclopentanone- d_4 and to Lamaty's value of 0.790 for K_H/K_D for formation of the bisulfite adduct for phenyl-2-propanone- d_5 .^{5,13}

Inserting the values of K_H/K_D into eq 3-5, we calculate $k_\alpha^2 = 1.071 \pm 0.030$ (1.035 ± 0.014 per deuterium), and $k_\beta^3 = 1.166 \pm 0.070$ (1.052 ± 0.010 per deuterium). The comparable values in the pinacol rearrangement of 1,1-diphenyl-2-methylpropane-1,2-diol are 1.195 for CD_3 migration (1.061 per deuterium) and 0.970 for CD_3 as the nonmigrating group (0.990 per deuterium).⁴

The isotope effect on the migrating group in the Baeyer-Villiger reaction is smaller than expected; the general trend predicts a larger per deuterium isotope effect for RCH_2 than for CH_3 .¹ This is consistent with a smaller decrease in the HCH bending force constant or a larger increase in HCO bending force constant for benzyl migration in the Baeyer-Villiger reaction than for methyl migration in the pinacol reaction. This implies less positive charge delocalized onto the migrating group in the former reaction. The large positive β isotope effect for CD_3 is definitive; it must be due to $\text{C}=\text{O}$ or $\text{C}=\text{OH}^+$ bond formation¹⁴ in the transition state for breakdown of the tetrahedral intermediate. In the pinacol reaction the β isotope effect is not significantly different from 1.0. This suggests a later transition state for migration of benzyl in the Baeyer-Villiger reaction than for methyl migration in the pinacol rearrangement.

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(14) Proton transfer steps in the Baeyer-Villiger reaction in nonprotic media remain to be elucidated. Proton transfer to the trifluoroacetate carbonyl simultaneous with the departure of that group during the



migration step would lead to $\text{C}=\text{O}$ and not $\text{C}=\text{OH}^+$ formation.

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Uses of Benzocyclopropenes in Synthesis. Catalysis by Silver Ion

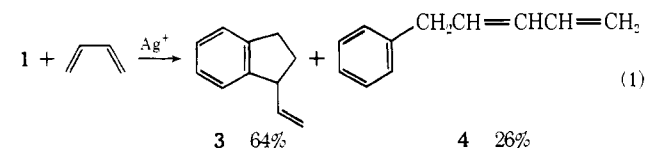
Sir:

Since the novel hydrocarbons benzocyclopropene (1)^{1a} and naphtho[b]cyclopropene (2)^{1b} have become



readily available, we have been studying their chemistry and report here some of our results.² Particularly interesting are the silver ion catalyzed reactions of these hydrocarbons with various substrates.³

Thus, reaction of 1 with butadiene and 1 mole % $\text{Ag}(\text{I})$ in benzene (0° , 30 min) gives 3 and 4 (eq 1).⁴



These products are rationalized in terms of intermediates 5 and 6 (Scheme I). In this scheme, 3 and 4 arise from 6 by ring closure and proton transfer, respectively.⁵ In contrast, the thermally induced reaction of 1 and buta-

(1) (a) E. Vogel, W. Grimme, and S. Korte, *Tetrahedron Lett.*, 3625 (1965); W. E. Billups, A. J. Blakeney, and W. Y. Chow, *Chem. Commun.*, 1461 (1971); (b) W. E. Billups and W. Y. Chow, *J. Amer. Chem. Soc.*, 95, 4099 (1973).

(2) For a review on benzocyclopropenes, see B. Halton, *Chem. Rev.*, 73, 113 (1973).

(3) Cleavage of strained carbon-carbon σ bonds with transition metals has been investigated extensively; however, much less is known about the metal-catalyzed reactions of these systems with other substrates. Exceptions are found when protic solvents are used where ready solvent incorporation is observed. For relevant references see H. Hogeveen and H. C. Volger, *J. Amer. Chem. Soc.*, 89, 2486 (1967); W. Merk and R. Pettit, *ibid.*, 89, 4788 (1967); T. J. Katz and S. A. Cerefice, *ibid.*, 91, 2405, 6519 (1969); R. Askani, *Tetrahedron Lett.*, 3349 (1970); N. B. Chapman, J. M. Key, and K. J. Toyne, *ibid.*, 5211 (1970); L. Cassar, P. E. Eaton, and J. Halpern, *J. Amer. Chem. Soc.*, 92, 3515, 6366 (1970); L. Cassar and J. Halpern, *Chem. Commun.*, 1082 (1970); K. G. Powell and F. J. McQuillin, *Tetrahedron Lett.*, 3313 (1971); R. Grigg and G. Shelton, *Chem. Commun.*, 1247 (1971); M. Sakai and S. Masamune, *J. Amer. Chem. Soc.*, 93, 4610, 4611 (1971); R. Noyori, T. Suzuki, Y. Kumagai, and H. Takaya, *ibid.*, 93, 5894, 5896 (1971); L. A. Paquette, *Accounts Chem. Res.*, 4, 280 (1971); L. A. Paquette and S. E. Wilson, *J. Amer. Chem. Soc.*, 93, 5934 (1971); L. A. Paquette, R. P. Henzel, and S. E. Wilson, *ibid.*, 93, 2335 (1971); W. G. Dauben and A. J. Kielbania, Jr., *ibid.*, 94, 3669 (1972); R. J. Roth and T. J. Katz, *ibid.*, 94, 4770 (1972); P. G. Gassman and T. Nakai, *ibid.*, 94, 5497 (1972); P. G. Gassman and F. J. Williams, *J. Chem. Soc., Chem. Commun.*, 80 (1972); *J. Amer. Chem. Soc.*, 94, 7733 (1972); P. G. Gassman, G. R. Meyer, and F. J. Williams, *ibid.*, 94, 7741 (1972); P. G. Gassman and T. J. Atkins, *ibid.*, 94, 7748 (1972); P. G. Gassman, T. J. Atkins, and J. T. Lumb, *ibid.*, 94, 7757 (1972); N. Acton, R. J. Roth, T. J. Katz, J. K. Frank, C. A. Maier, and I. C. Paul, *ibid.*, 94, 5446 (1972); L. A. Paquette and L. M. Leichter, *ibid.*, 94, 3653 (1972); L. A. Paquette, S. E. Wilson, R. P. Henzel, and G. R. Allen, Jr., *ibid.*, 94, 7761 (1972); L. A. Paquette, S. E. Wilson, and R. P. Henzel, *ibid.*, 94, 7771 (1972); L. A. Paquette, R. P. Henzel, and S. E. Wilson, *ibid.*, 94, 7780 (1972), and references therein.

(4) Spectral properties of 3 are: nmr (CCl_4) δ 1.6-2.6 (m, 2 H), 2.86 (d of d, 2 H, $J = 6$, $J = 9$ Hz), 3.7 (q, 1 H, $J = 9$ Hz), 4.89-5.3 (m, 2 H), 5.46-6.2 (m, 1 H), and 7.18 (s, 4 H); ir (neat) 910, 990, and 1638 cm^{-1} . 4 shows nmr signals at δ 3.51 (d, 2 H, $J = 8$ Hz), 4.85-5.48 (m, 2 H), 5.48-7.0 (m, 2 H), and 7.2 (s, 5 H); uv $\lambda_{\text{max}}^{\text{C}_6\text{H}_6}$ 229 nm (ϵ 20,000). The ir is in good agreement with the one reported by Prévost for this compound. See C. Prévost, P. Miginiac, and L. Miginiac-Groizeleau, *Bull. Soc. Chim. Fr.*, 10, 2485 (1964).

(5) Although formation of carbon-silver σ bonds is frequently invoked³ in rearrangements of strained hydrocarbons which are catalyzed by silver ion, it should be noted that few compounds incorporating this structural feature have been reported.