sequence that proceeds without rearrangement in the dicyclopentadiene system.[17]

Anal. Calcd for $C_9H_{14}O_2$: C, 70.13; H, 9.09. Found: C, 69.90; H, 9.22.

Methanesulfonate 3b. The mesylate was prepared by reaction of a slight excess of methanesulfonyl chloride with **3c** in pyridine in the cold. The ester, recrystallized from methanol, had mp 105.5–106.0°.

Anal. Calcd for $C_{10}H_{16}O_4S$: C, 51.75; H, 6.90; S, 13.78. Found: C, 51.72; H, 6.95; S, 13.71.

8-*exo*-Hydroxy-*exo*-4-oxatricyclo[5.2.1.$0^{2,6}$]decane (4c). Following the procedure used for the preparation of **3c**, 10.0 g of pure *exo*-4-oxatricyclo[5.2.1.$0^{2,6}$]-8-decene[4] yielded 5.28 g (47%) of **4c**, bp 87.5° (0.25 mm)–90° (0.30 mm) [lit.[4] bp 95–97° (0.7 mm).

Methanesulfonate 4b. The mesylate, prepared from **4c** in the manner described for **3b**, formed shiny white platelets, mp 56.4–56.7°, after recrystallization from petroleum ether (bp 30–60°).

Anal. Calcd for $C_{10}H_{16}O_4S$: C, 51.75; H, 6.90; S, 13.78. Found: C, 51.87; H, 6.99; S, 13.75.

Methanesulfonate 5b. The ester, prepared from the alcohol 8-*exo*-hydroxy-*endo*-tricyclo[5.2.1.$0^{2,6}$]decane (**5d**)[19] and methanesulfonyl chloride in pyridine, was an oil which decomposed upon distillation.

In a second preparation, the reaction mixture from 5.0 g of alcohol **5d** and 5.0 g of methanesulfonyl chloride in 40 ml of anhydrous pyridine was stored in a freezer overnight and then was poured over ice to which had been added 46 ml of concentrated HCl. The orange oil which separated was taken up in ether and the aqueous portion was extracted three times with ether. The combined ethereal portions were washed twice with water, dried over $MgSO_4$, and then filtered. After removal of solvent, a final removal was conducted under high vacuum at room temperature. The yield was 6.8 g (90%) of ester as a slightly discolored liquid.

Anal. Calcd for $C_{11}H_{18}SO_3$: C, 57.45; H, 7.83. Found: C, 57.75; H, 7.90.

Kinetic Measurements. Reagent grade *p*-dioxane was rigorously purified by the method of Wiberg.[20] Typically 45.0 g of dioxane was diluted with 15.0 g of deionized water to prepare the 75% aqueous dioxane. Esters were weighed into 50-ml volumetric flasks so that solutions approximately 1×10^{-2} *M* in ester would be obtained when solvent was added. The samples were divided into ten screw-cap test tubes and incubated in a constant-temperature bath together with a 5-ml solvent blank. Samples were withdrawn at intervals, frozen in Dry Ice–acetone, washed out with water, and titrated immediately with 1×10^{-2} *M* NaOH to a phenolphthalein end point. Infinity values for **5b** and **3b** were constant at 100 and 90% of theoretical, respectively; the theoretical infinity value for **4b** was used after it was discovered that solvent, alone or pyridine buffered, developed considerable acidity over the reaction time required for 10 half lives. Plots of log $(A_\infty - A_t)$ *vs.* time were linear; the slopes were determined by calculation of the least-squares line fitting the experimental points.

Product analysis was accomplished by gas chromatography on a 5 ft × 0.125 in. 20% FFAP column at 180° with a flow rate of 25 ml/min. Samples taken at various times from kinetic runs at different temperatures showed essentially constant ratios of **3c** and **4c**, depending on the starting ester; no traces of the endo epimers of **3c** and **4c** (independently synthesized) were detected. In an experiment to recover unreacted **3c**, 150 mg of ester in 50 ml of solvent was incubated at 75.90° for 7–8 min, poured into ice water, and extracted continuously with ether. After drying and evaporation, crystals, mp 100–102.5°, were recovered: ir spectrum identical with that of authentic **3c**; mmp with **3c**, 88–93°; mmp with **4c**, 40–93°. Similarly 150 mg of **4c** in 50 ml of solvent was incubated at 75.90° for 4.5 hr, poured into ice water, and extracted. Crystals melting at 55.2–56.2° were recovered: ir spectrum identical with that of authentic **4c**; mmp with **4c**, 55.0–56.0°; mmp with **3c**, 40–68°.

Registry No. 3b, 43187-55-9; **3c**, 43187-56-0; **4b**, 43187-57-1; **4c**, 43187-58-2; **5b**, 43187-59-3; **5d**, 10271-45-1; **7**, 43187-61-7; *exo*-4-oxatricyclo[5.2.1.$0^{2,6}$]-8-decene, 43187-62-8.

References and Notes

(1) National Science Foundation Predoctoral Fellow, 1970–1972.
(2) R. F. Gratz and P. Wilder, Jr., *Chem. Commun.*, 1449 (1970).
(3) D. J. Cash, Ph.D. Dissertation, Duke University, 1964.
(4) C. F. Culberson, J. H. Seward, and P. Wilder, Jr., *J. Amer. Chem. Soc.*, **82**, 2541 (1960).
(5) For reviews of neighboring-group assistance see W. Lwowski, *Angew. Chem.*, **70**, 483 (1958); B. Capon, *Quart. Rev., Chem. Soc.*, **18**, 45 (1964).
(6) (a) M. Cinquini, S. Colonna, and F. Montanari, *Tetrahedron Lett.*, 3181 (1966); (b) H. Hogeveen, G. Maccagnani, and F. Montanari, *J. Chem. Soc. C*, 1585 (1966).
(7) (a) C. N. Lieske, E. G. Miller, Jr., J. J. Zeger, and G. M. Steinberg, *J. Amer. Chem. Soc.*, **88**, 188 (1966); (b) J. S. Brimacombe, F. Hunedy, and L. C. N. Tucker, *J. Chem. Soc. C*, 1381 (1968); (c) M. S. Newman and A. L. Leegwater, *J. Amer. Chem. Soc.*, **90**, 4410 (1968); (d) H. D. Burrows and R. M. Topping, *Chem. Commun.*, 904 (1969).
(8) (a) D. L. H. Williams, *Tetrahedron Lett.*, 2001 (1967); (b) L. A. Paquette and R. W. Begland, *J. Amer. Chem. Soc.*, **90**, 5159 (1968); (c) B. Capon, S. T. McDowell, and W. V. Raftery, *Chem. Commun.*, 389 (1971); (d) M. Miljkovic, D. Miljkovic, A. Jokic, V. Andrejevic, and E. A. Davidson, *J. Org. Chem.*, **37**, 2536 (1972).
(9) (a) E. Allred and S. Winstein, *J. Amer. Chem. Soc.*, **89**, 3991, 3998, 4008, 4012 (1967); (b) J. R. Hazen and D. S. Tarbell, *Tetrahedron Lett.*, 5927 (1968); (c) J. R. Hazen, *ibid.*, 1897 (1969).
(10) (a) N. A. Hughes and P. R. H. Speakman, *J. Chem. Soc. C*, 1182 (1967); (b) C. F. Gibbs and H. J. Jennings, *Can. J. Chem.*, **48**, 2734 (1970); (c) J. S. Brimacombe and O. A. Ching, *J. Chem. Soc. C*, 1642 (1968); (d) *ibid.*, 964 (1969); (e) *Carbohyd. Res.*, **9**, 287 (1969).
(11) J. C. Martin and P. D. Bartlett, *J. Amer. Chem. Soc.*, **79**, 2533 (1957).
(12) (a) L. A. Paquette and P. C. Storm, *J. Org. Chem.*, **35**, 3390 (1970); (b) L. A. Paquette and M. K. Scott, *J. Amer. Chem. Soc.*, **94**, 6760 (1972); (c) L. A. Paquette, I. R. Dunkin, J. P. Freeman, and P. C. Storm, *ibid.*, **94**, 8124 (1972).
(13) (a) P. G. Gassman and J. L. Marshall, *Tetrahedron Lett.*, 2429, 2433 (1968); (b) P. G. Gassman and J. G. MacMillan, *J. Amer. Chem. Soc.*, **91**, 5527 (1969).
(14) T. Tsuji, T. Komeno, H. Itani, and H. Tanida, *J. Org. Chem.*, **36**, 1648 (1971).
(15) K. Takeuchi, T. Oshika, and Y. Koga, *Bull. Chem. Soc. Jap.*, **38**, 1318 (1965).
(16) P. v. R. Schleyer and C. J. Lancelot, *J. Amer. Chem. Soc.*, **91**, 4297 (1969).
(17) G. W. Wright, Ph.D. Dissertation, Duke University, 1971.
(18) H. C. Brown and P. J. Geoghegan, Jr., *J. Org. Chem.*, **35**, 1844 (1970).
(19) S. J. Cristol, W. K. Seifert, and S. B. Soloway, *J. Amer. Chem. Soc.*, **82**, 2351 (1960).
(20) K. B. Wiberg, "Laboratory Technique in Organic Chemistry," McGraw-Hill, New York, N. Y., 1960.

Rate–Strain Relationships in the Oxidation of Small-Ring Cyclic Olefins with Peracid

Louis E. Friedrich* and Rocco A. Fiato[1]

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

Received October 9, 1973

The kinetics of epoxidation of only two strained olefins have been reported in the literature.[2a-c] In peracetic–acetic acid solution at 25.8°, cyclobutene epoxidizes 6.3 times slower than cyclohexene and 9.6 times slower than cyclopentene.[3] Norbornene, on the other hand, epoxidizes 1.2 times faster than cyclohexene at 25° with perlauric acid in chloroform.[4] Since norbornene epoxidizes 99.5% exo,[5] the corrected rate constant for norbornene per olefin side is 2.4 times faster than cyclohexene. Even though cyclobutene and norbornene are 30.6 and 27.2 kcal/mol strained,[6] their rate constants for epoxidation are within a factor of 10 (1.25 kcal/mol) of the rate constants for the much lesser strained cyclopentene through cycloheptene systems.[2a] There appears to be no rate–strain relationship for epoxidation reactions.

In light of the above results, we expected that the oxidation of cyclopropenes with peracid might be atypical and would be a severe test of the previously observed results that the rate of epoxidation is independent of olefin strain. Specifically, the 55 kcal/mol strain[6] in cyclopropenes is twice the strain of the olefins whose epoxidation kinetics have previously been studied. Furthermore, this abnormally large strain has caused the double bond in these compounds to have a characteristic high reactivity toward various reagents.[7] If the loss of even a fraction of this 55 kcal/mol of strain energy were not compensated by

an increase in the transition-state strain for peracid oxidation, cyclopropenes would be quite reactive. Also, our past experiences with the sensitivity of cyclopropenes to air oxidation suggested that they might react "like a shot" with oxidizers such as peracid.

In order to evaluate the reactivity of cyclopropenes, we have determined the peracid oxidation kinetics for 1,2-diphenylcyclopropene (1)[8] and the 1,2-diphenyl analogs of cyclobutene (2)[9] and cyclopentene (3).[10] Cyclopentene 3 gave a quantitative yield of epoxide when reacted with peracid. Cyclobutene 2 gave the expected epoxide 4 as the only reaction product at short reaction times. After longer times, 1,2-dibenzoylethane 5[9] was the major product of the reaction. For the purposes of this work, the details of this interesting oxidation were not investigated. Last, cyclopropene 1 gave a quantitative yield of 1,2-diphenyl-2-propen-1-one.[11] This product was expected, since the oxidation of other cyclopropenes gave enone products.[12]

The kinetics for olefins 2 and 3 were determined titrimetrically by following peracid disappearance and checked to be overall second order. The cyclobutene runs were terminated before significant amounts of diketone 5 were formed. Competitive kinetic runs between cyclopropene 1 and cyclobutene 2 were used to get the rate constant of the cyclopropene oxidation relative to cyclobutene 2. The standard second-order competitive kinetics analysis as described by Russell[13] was used.

As shown in Table I, there is an 11.7-fold decrease in the rate constant for cyclobutene 2 relative to cyclopentene 3, similar to the 9.6-fold decrease in the unsubstituted system which was previously reported.[3] Surprisingly, however, cyclopropene 1 does *not* oxidize faster than olefins 2 and 3. The rate constant is indistinguishable from that for cyclobutene 2.

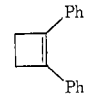
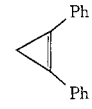
Oxidation with peracid appears to be the first reported reaction in which a cyclopropene has exhibited a similar reactivity in comparison to larger ring analogs. This result seems consistent with an oxabicyclobutane-forming transition state where the activation increase in strain is similar to that experienced by relatively unstrained olefins such as cyclopentene.[14] The present study has severely tested and strengthened the postulate that the rate of epoxidation *is* independent of olefin strain.

Even though the postulate has been found to be operationally correct for cyclopropenes, a thorough analysis of the epoxidation rate-strain problem reveals some inconsistencies. Specifically, the difference in strain between bicyclobutanes and cyclopropenes is *ca.* 12 kcal/mol whereas the strain difference between bicyclo[2.1.0]pentanes (or 5-oxabicyclo[2.1.0]pentanes) and cyclobutenes is *ca.* 24 kcal/mol.[6] As a result, if oxabicyclobutanes possess about the same strain as bicyclobutanes,[15] the activation increase in strain for an oxabicyclobutane-forming transition state could be considerably less than that experienced in the epoxidation of cyclobutenes. This situation should lead to a faster rate for cyclopropene epoxidation if the transition state is moderately advanced. In contrast, bicyclo[3.1.0]hexanes (and presumably 6-oxabicyclo[3.1.0]hexanes) are *ca.* 27 kcal/mol more strained than cyclobutenes.[6] As such, the epoxidation rates for cyclopentenes and cyclobutenes should be similar, as observed.

A way out of this dilemma is to postulate an early transition state for epoxidation that does not yet reflect any activation in strain. However, this would not be in agreement with the moderate vinyl and allylic substituent effects that have been observed for alkene epoxidations.[2a] We have also observed similar moderate substituent effects in the oxidation of cyclopropenes with peracids.[16]

In conclusion, we believe that one or more of the premises given above must be wrong. One little-tested premise is that the strain of heteroatomic substituted systems is the same as their all-carbon analogs. If oxabicyclobutanes were considerably more strained than bicyclobutanes, the anticipated rate of cyclopropene epoxidation might be reduced to that observed.

Table I
Rate Constants of *m*-Chloroperbenzoic Acid Oxidation of Olefins 1–3 in CCl_4 at 0°

	Olefin	$10^3 k_2$, M^{-1} sec^{-1} [a]	Rel k_2
3		38.8 ± 2.3 (8)[b]	11.7
2		3.32 ± 0.05 (3)[b]	(1.0)
1		3.4 ± 0.1 (9)[c]	1.0

[a] 0.01–0.03 *M* olefin, 0.006–0.1 *M* peracid. Errors are standard deviations of independent runs with the indicated degrees of freedom. [b] Measured titrimetrically following peracid. [c] Competitive runs following the relative disappearance of olefins 1 and 2 by nmr.

Experimental Section

General. 1,2-Diphenylcyclopropene (1),[8] 1,2-diphenylcyclobutene (2),[9] and 1,2-diphenylcyclopentene (3)[10] were all purified by recrystallization from cold anhydrous methanol. The physical and spectral data obtained from these samples were identical with those previously reported.

Product studies and kinetic runs were performed with Mallinkrodt SpectrAR grade CCl_4 from freshly opened bottles. *m*-Chloroperbenzoic acid (Aldrich) was purified by washing with a neutral phosphate buffer in order to remove *m*-chlorobenzoic acid.[17]

1,2-Diphenylcyclopropene (1) with *m*-Chloroperbenzoic Acid. A solution of 10 mg (0.05 mmol) of cyclopropene 1, 10 μl of CH_2Cl_2, and 6 mg (0.03 mmol) of 99% *m*-chloroperbenzoic acid was prepared at 0° in CCl_4. After a negative starch–iodide test was obtained the solution was analyzed by nmr (CH_2Cl_2 as internal standard) and showed a 1:1 mixture of olefin and 1,2-diphenyl-2-propen-1-one.

The enone prepared in the above reaction and authentic 1,2-diphenyl-2-propen-1-one[11] were both analyzed: ir (CCl_4) 1668 cm^{-1}; nmr (CCl_4) δ 8.10–7.70 (m, 2), 7.55–7.10 (m, 8), 5.98 (s, 1), 5.54 (s, 1).

When olefin 1 was treated with a slight excess of peracid the nmr spectrum (CCl_4) of the product mixture showed an apparent AB quartet (J = 6.0 Hz) centered at δ 3.20 which also appeared in the spectrum of 1,2-diphenyl-2-propen-1-one that had been treated with peracid. This was presumably due to formation of the epoxide of the enone.

1,2-Diphenylcyclobutene with *m*-Chloroperbenzoic Acid. A solution of 20 mg (0.10 mmol) of cyclobutene 2 in 2.0 ml of CCl_4 was cooled to 0° and treated with 9 mg (0.05 mmol) of *m*-chloroperbenzoic acid. After a negative starch–iodide test was obtained the mixture was washed with 10% aqueous $NaHCO_3$, dried over anhydrous K_2CO_3, and concentrated on a rotary evaporator. The sample was analyzed by nmr and showed an apparent A_2B_2 multiplet centered at δ 2.52 as the only new peaks in the region δ 0.0–5.0. Analysis of the spectrum indicated that *ca.* 50% conversion (100% yield) of olefin 2 to epoxide 4 had occurred. Samples of epoxide 4 could not be obtained in greater than 80+ % purity (with olefin 2 as the only contaminant) by silica gel chromatography or by vpc with columns containing 4% KOH.

The enriched sample of epoxide 4 was analyzed: ir (CCl_4) 1660–1680 cm^{-1} (transparent); nmr (CCl_4) δ 7.40 (m, 10), 2.52 (apparent A_2B_2 m, 4); mass spectrum (70 eV) m/e 222 (molecular ion).

When cyclobutene 2 was treated with a slight molar excess of peracid, 1,2-dibenzoylethane (5) was isolated in high yield: mp 146–148° (lit.[9] mp 146.5–148.5°); ir (CCl_4) 1680 cm^{-1}; nmr (CCl_4)

δ 7.90 (m, 4), 7.30 (m, 6), 3.30 (s, 4); mass spectrum (70 eV) *m/e* 238 (68, molecular ion), 105 (100).

When the mixture of olefin **2** and epoxide **4** was worked up under acidic conditions, new absorptions in the nmr (CCl_4) at δ 1.50–1.30 (m) and the ir (CCl_4) at 1674 cm^{-1} were observed. These were presumably due to the rearrangement[2a] of epoxide **4** to 1-benzoyl-1-phenylcyclopropane [lit.[18] ir (CCl_4) 1675 cm^{-1}; nmr (CCl_4) 7.4 (m, 10), 1.40 (apparent A_2B_2 m, 4)].

1,2-Diphenylcyclopentene (3) with *m*-Chloroperbenzoic Acid. A solution of 220 mg (1.00 mmol) of cyclopentene **3** in 3.0 ml of CCl_4 was treated with 180 mg (*ca.* 1.00 mmol) of *m*-chloroperbenzoic acid for 36 hr at 0°. The resulting mixture was filtered, washed with 10% aqueous $NaHCO_3$, dried over anhydrous K_2CO_3, and concentrated on a rotary evaporator. The crude product thus obtained was analyzed: ir (CCl_4) 1600–1750 cm^{-1} (transparent); nmr (CCl_4) δ 6.88 (s, 10) 2.10 (apparent broad d, J = 6.0 Hz, 4), 1.65 (apparent broad q, J = 5.0 Hz, 2); mass spectrum (70 eV) *m/e* 236 (molecular ion).

Nmr Method of Determining Rate Constants. A stock solution was prepared of cyclopropene **1** (*ca.* 0.08 *M*) and cyclobutene **2** (*ca.* 0.04 *M*) with CH_2Cl_2 and $PhCH_3$ as internal standards. The solution was analyzed to determine the initial (olefin/internal standard) integration ratios. The nmr tube was then cooled to 0° and an equal volume of *ca.* 0.075 *M* peracid stock solution was added. The tube was stored at 0° for 12–20 hr and then analyzed by nmr to determine the final (olefin/internal standard) integration ratios.

Each peak was integrated 8–12 times with the average integration value used in subsequent calculations. The relative rates were determined from the following equation[13]

$$\frac{k(1)}{k(2)} = \frac{\ln (\text{fraction 1 remaining})}{\ln (\text{fraction 2 remaining})}$$

where $k(1)/k(2)$ is the ratio of the second-order rate constants for olefins **1** and **2**, respectively, and the fraction **1** (or **2**) remaining at time t is the final time ratio (olefin$_t$/internal standard) divided by the initial ratio (olefin$_0$/internal standard).

Iodometric Method of Determining Rate Constants. A magnetically stirred solution containing known amounts of olefin and peracid was prepared at 0° in a 10-ml volumetric flask. A short time thereafter (1–2 min to allow mixing and thermal equilibration), a 1-ml aliquot was withdrawn with a calibrated (at 0°) syringe which was cooled to 0°. The aliquot was added to a solution of 1 ml of acetic acid and 1 ml of 10% aqueous KI. The liberated iodine was titrated with $Na_2S_2O_3$ (*ca.* 1×10^{-3}–1×10^{-4} *M*) which had been previously normalized with KIO_3. A stopwatch was started during the addition of the reaction solution to the acetic acid–KI solution. The peracid loss during the initial 1–2-min period from the prepared concentration was calculated and an appropriate correction was made in the time zero olefin concentration used in subsequent calculations.

The reaction solution was subsequently monitored at recorded times by withdrawing 0.5- or 1.0-ml aliquots with a chilled (0°), calibrated syringe. Ice was replaced in the cooling bath to maintain a temperature of 0°. The reaction solution was analyzed repeatedly until 20–60% peracid loss was noted. Usually, several (5–12) samples were analyzed at various times for each run.

The data were analyzed first by a least-squares program on a Hewlett-Packard Model 9820-A advanced programming calculator. The normal second-order rate equation was rearranged into terms of observables, for conditions of initial olefin concentration greater than initial peracid concentration

$$(1/A_\infty) \ln (2V_aA_\infty/M\text{ml}_t + 1) = (1/A_\infty) \ln (2V_aA_\infty/M\text{ml}_0 + 1) + k_2t$$

where A_∞ is the difference in the time zero concentration of olefins and peracid, respectively, V_a is the volume in milliliters of the reaction aliquot analyzed, M is the molarity of the thiosulfate stock solution, and ml$_t$ and ml$_0$ are the volumes of thiosulfate solution at time t and t_0 required to titrate the liberated iodine for the respective samples.

Subsequently, the data were analyzed with a nonlinear iterative least-squares computer program[19] on an IBM 360/65 computer. This program accounts for random errors present in all observables. In all cases, the data gave linear plots with the second-order rate equation and the rate constants were invariant over a varying range of initial reactant concentrations.

Acknowledgments. We thank the National Science Foundation and the Merck Co. Foundation for financial support of this work. We also thank the University of Rochester Computing Center for computer time.

Registry No.—**1**, 24168-52-3; **2**, 3306-02-3; **3**, 1485-98-9; **4**, 43187-63-9; **5**, 495-71-6; **6**, 43187-64-0; *m*-chloroperbenzoic acid, 937-14-4; 1,2-diphenyl-2-propen-1-one, 4452-11-3.

References and Notes

(1) Elon Huntington Hooker Fellow, 1972–1973.
(2) (a) For a review of peracid oxidation of olefins, see D. Swern in "Organic Peroxides," Vol. II, D. Swern, Ed., Wiley-Interscience, New York, N. Y., 1971, pp 355–535. (b) For a review of electrophilic additions to strained olefins, see T. G. Taylor, *Accounts Chem. Res.*, **2**, 152 (1969). (c) G. Colin, *et al.*, *J. Prakt. Chem.*, **311**, 238 (1969).
(3) D. Swern, *J. Amer. Chem. Soc.*, **69**, 1692 (1947).
(4) K. D. Bingham, G. D. Meakins, and G. H. Whitham, *Chem. Commun.*, 445 (1966).
(5) H. C. Brown, J. H. Kawakami, and K.-T. Liu, *J. Amer. Chem. Soc.*, **95**, 2209 (1973).
(6) P. v. R. Schleyer, J. E. Williams, and K. R. Blanchard, *J. Amer. Chem. Soc.*, **92**, 2377 (1970).
(7) (a) For the same reason that the heat of hydrogenation of cyclopropenes is *ca.* 27 kcal/mol more exothermic than the heat of hydrogenation of other olefins, see (b) G. L. Closs in "Advances in Alicyclic Chemistry," H. Hart and G. J. Karabatsos, Ed., Academic Press, London, 1966, p 53.
(8) We thank Dr. Donald H. Wadworth of Eastman Kodak Co., Rochester, N. Y., for a sample of known cyclopropene **1**; see D. T. Longone and D. M. Stehouwer, *Tetrahedron Lett.*, 1016 (1970).
(9) We thank Professor R. H. Schlessinger of the University of Rochester for providing a sample of known cyclobutene **2** and diketone **5**; see R. M. Dodson and F. G. Zielske, *J. Org. Chem.*, **32**, 28 (1967).
(10) R. Criegee, A. Kerckow, and H. Zinke, *Chem. Ber.*, **88**, 1878 (1955).
(11) J. Matti and M. Perrier, *Bull. Soc. Chim. Fr.*, **22**, 525 (1955).
(12) L. E. Friedrich and R. A. Cormier, *Tetrahedron Lett.*, 4761 (1971), and references cited therein.
(13) G. A. Russell in "Techniques of Organic Chemistry," Vol. VIII, S. L. Freiss, E. S. Lewis, and A. Weissberger, Ed., Interscience, New York, N. Y., 1961, p 343.
(14) A. K. Awasthy and J. Rocek, *J. Amer. Chem. Soc.*, **91**, 991 (1969).
(15) The strains of ethylene oxide, oxetane, and tetrahydrofuran, respectively, are the same as for their all carbon analogs; see A. S. Pell and G. Pilcher, *Trans. Faraday Soc.*, **61**, 71 (1965).
(16) Unpublished results of L. E. Friedrich and R. A. Fiato, Department of Chemistry, University of Rochester, Rochester, N. Y.
(17) N. N. Schwartz and J. H. Buembergs, *J. Org. Chem.*, **29**, 1976 (1964).
(18) G. W. Griffin and R. B. Hager, *J. Org. Chem.*, **28**, 600 (1963).
(19) L. E. Friedrich, unpublished program, University of Rochester, 1969.

Synthesis of *cis*- and *trans*-1-(3,4-Dimethoxybenzyl)-3,7-dimethyl-5,8-dimethoxy-1,2,3,4-tetrahydroisoquinoline. Observations on the Mechanism of the Bischler–Napieralski Reaction

Joseph Gal, Robert J. Wienkam, and N. Castagnoli, Jr.*

Department of Pharmaceutical Chemistry, School of Pharmacy, University of California, San Francisco, California 94143

Received September 18, 1973

Considerable interest has been expressed recently in the possible contribution that tetrahydroisoquinolines derived endogenously from dopamine and related phenylethylamines and aldehydes such as 3,4-dihydroxyphenylacetaldehyde and acetaldehyde may make to central and peripheral adrenergic mechanisms.[1] As part of our investigations into the metabolism of the hallucinogenic compound 1-(2,5-dimethoxy-4-methylphenyl)-2-aminopropane (**1**),[2] we wish to examine the possible endogenous formation of tetrahydroisoquinolines derived from amine **1** and aldehyde **3**. Such condensation reactions presumably proceed by a Pictet–Spengler cyclization.[3] As has been reported for several drugs containing aromatic OCH_3 groups,[4] we have detected both the 2-O- and 5-O-demethylated compounds **2a** and **2b**, respectively, in the urine of rabbits administered amine **1** intraperitoneally.[5] Since Pictet–Spengler cyclizations readily occur with phenylethylamines ac-