74-3; (*R*)-**11**, 49776-50-3; quinoxaline-2-carboxamide, 5182-90-1; 2-carboethoxyquinoxaline, 7065-23-8; quinoline, 91-22-5; quinaldine 91-63-4; (*RS*)-1,4-diacetyl-2-methyl-6-bromo-1,2,3,4-tetrahydroquinoxaline, 49849-75-4; (*S*)-1,4-diacetyl-2-methyl-6-bromo-1,2,3,4-tetrahydroquinoxaline, 49849-76-5.

References and Notes

(1) (a) Part XXI of this series: G. H. Fisher and H. P. Schultz, *J. Org. Chem.*, **39**, 631 (1974); (b) NSF Trainee 1969–1972; abstracted from the Ph.D. dissertation of G. H. F.
(2) S. J. Benkovic, P. A. Benkovic, and D. R. Comfort, *J. Amer. Chem. Soc.*, **91**, 5270 (1969); S. J. Benkovic, P. A. Benkovic, and R. Chrzanowski, *ibid.*, **92**, 523 (1970); S. J. Benkovic, W. P. Bullard, and P. A. Benkovic, *ibid.*, **94**, 7542 (1972).
(3) M. P. Mertes and A. J. Lin, *J. Med. Chem.*, **13**, 77 (1970).
(4) R. Aguilera, J.-C. Duplan, and C. Nofre, *Bull. Soc. Chim. Fr.*, 4491 (1968).
(5) E. Campaigne, N. F. Chamberlain, and B. E. Edwards, *J. Org. Chem.*, **27**, 135 (1962).
(6) V. A. Zagorevskii and N. V. Dudykina, *Zh. Obshch. Khim.*, **34**, 2282 (1964); *Chem. Abstr.*, **61**, 11960*f* (1964).
(7) K. Nagarajan, M. D. Nair, and P. M. Pillai, *Tetrahedron*, **23**, 1683 (1967).
(8) H. Booth, *J. Chem. Soc.*, 1841 (1964).
(9) J. S. Morley, *J. Chem. Soc.*, 4002 (1952).
(10) J. C. Cavagnol and F. Y. Wiselogle, *J. Amer. Chem. Soc.*, **69**, 795 (1947).
(11) D. P. N. Satchell, *Quart. Rev. (London)*, **17**, 160 (1963).
(12) R. A. Archer and H. S. Mosher, *J. Org. Chem.* **32**, 1378 (1967).
(13) D. G. Lister and J. K. Tyler, *Chem. Commun.*, 152 (1966).
(14) A. F. Holleman, *Recl. Trav. Chim.*, **25**, 183 (1906).
(15) G. H. Fisher, P. J. Whitman, and H. P. Schultz, *J. Org. Chem.*, **35**, 2240 (1970).
(16) G. S. Hammond and F. J. Modic, *J. Amer. Chem. Soc.*, **75**, 1385 (1953).
(17) R. Van Dusen and H. P. Schultz, *J. Org. Chem.*, **21**, 1326 (1956).
(18) G. F. Bettinetti, *Ann. Chim. (Rome)*, **51**, 920 (1961); *Chem. Abstr.*, **57**, 5914*c* (1962).
(19) F. Minisci, G. P. Gardini, R. Galli, and F. Bertini, *Tetrahedron Lett.*, 15 (1970).
(20) C. L. Butler and L. H. Cretcher, *J. Amer. Chem. Soc.*, **55**, 2605 (1933).
(21) M. Semonsky, A. Cerny, and V. Zikan, *Chem. Listy*, **50**, 116 (1956); *Collect. Czech. Chem. Commun.*, **21**, 382 (1956); *Chem. Abstr.*, **50**, 13059*a* (1956).
(22) R. S. Cahn, C. K. Ingold, and V. Prelog, *Experientia*, **12**, 81 (1956).
(23) Melting points, uncorrected, were determined on a Thomas-Hoover apparatus. Spectra were recorded as follows: uv, Jasco ORD/UV-5 in 95% ethanol in 1-cm quartz cells; H nmr, Hitachi Perkin-Elmer R-20, 60 MHz, 34°, or Varian Associates HA-100D-15, 100 MHz, 26°, δ in ppm from internal TMS; ir, Beckman IR-10. All optical activities were recorded on a Rudolph Model 63 polarimeter. Elemental analyses were performed by PCR, Inc., Gainesville, Fla. Ligroin was medium boiling, bp 66–75°, and EtOH was 95%. Tosyl chloride was recrystallized from THF. Pyridine was redistilled from CaH_2 and stored over NaOH pellets. Anhydrous ether was dried over $LiAlH_4$.
(24) A. S. Elina and O. Yu. Magidson, *J. Gen. Chem. USSR*, **25**, 145 (1955); *Chem. Abstr.*, **50**, 1839*g* (1956).
(25) H. Adkins and H. R. Billica, *J. Amer. Chem. Soc.*, **70**, 695 (1948).
(26) W. L. Graef, J. C. Cannon, and J. P. Buckley, *J. Med. Chem.*, **8**, 260 (1965).
(27) K. Böttcher, *Ber.*, **46**, 3084 (1913).
(28) M. Munk and H. P. Schultz, *J. Amer. Chem. Soc.*, **74**, 3433 (1952).
(29) S. Maffei and S. Pietra, *Gazz. Chim. Ital.*, **88**, 556 (1958); *Chem. Abstr.*, **53**, 20060*d* (1959).
(30) C. Ris, *Ber.*, **21**, 383 (1888).

Sigmatropic Rearrangement of Unsaturated Acetals. A Mechanistic Study of the Thermal Isomerization of 5-Alkylidene-1,3-dioxanes

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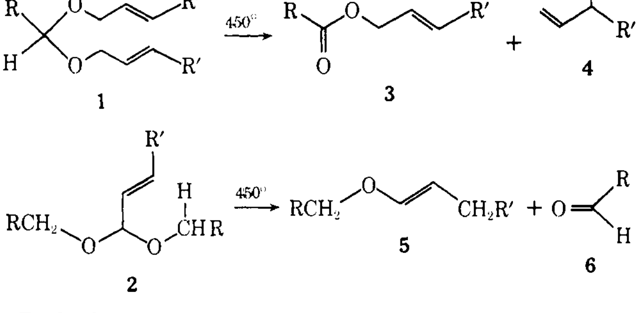
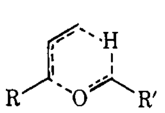
The preparation and pyrolysis of 2-*tert*-butyl-5-ethylidene-1,3-dioxane-2-*d* are described. A negative isotope crossover experiment and a deuterium kinetic isotopic effect are in favor of an intramolecular isomerization involving a concerted 1,5-hydrogen shift. Some conclusions on the transition state are discussed.

We have shown that unsaturated acetals undergo two types of thermal cleavage depending on the location of the double bond.[2] The acetals of type **1** derived from allylic alcohols cleave thermally to give allylic esters **3** and olefins **4**. On the other hand, those acetals **2** derived from α,β-unsaturated aldehydes fragment to vinyl ethers **5** and saturated aldehydes **6**.



Both cleavages can be described as retro-ene reactions[3a] or retrograde $_{\pi}2_{\sigma}2_{s} + {}_{\pi}2_{s}$ cycloadditions in which a heteroatom is involved. For acyclic acetals, the results of kinetic studies in the gas-phase pyrolysis[3b] (first-order kinetics with a negative activation entropy) unambiguously support a concerted [1,5] sigmatropic hydrogen migration. The structures of cleavage products are in agreement with such a mechanism. The experimental data available to date suggest that a six-membered transition state (such as **7a** or **7b**) is involved in the thermolysis.



7a, R = O-alkyl; R′ = H, alkyl
b, R = H; R′ = O-alkyl

Insofar as acyclic acetals are concerned, there is no steric restriction to such a transition state. In cyclic acetals, such as 5-alkylidene-1,3-dioxanes **8**, the concerted [1,5] sigmatropy, as proposed above, imposes considerable strain on the less favored[4] boat conformer **9**. Dreiding

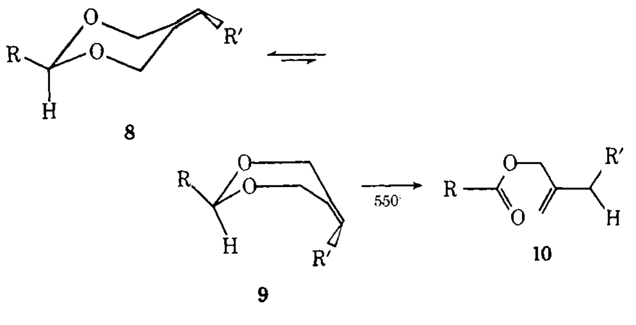


Table I
The Kinetic Isotopic Effect in the Pyrolysis of 18

Conditions of pyrolysis[a]	Deuterium content, %: Starting dioxane **18**, D_s	Deuterium content, %: Recovered dioxane **18**, D_r	Deuterium content, %: Ester **20**	k_H/k_D[b] at 510°
510, 45 sec, 50%	36.4	49.4	28.5	2.3
510, 45 sec, 45%	20.6	30.9	12.4	3.9

[a] Temperature (°C), contact time in seconds, total conversion of the labeled **18**. [b] See Experimental Section.

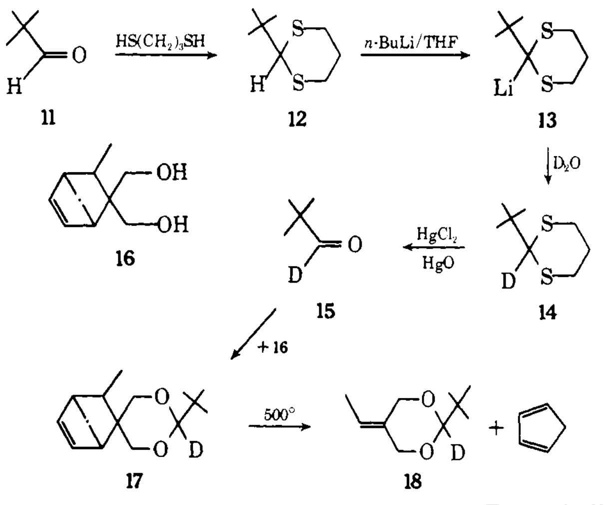
models of this conformation show that the migrating hydrogen atom is positioned 3 Å away from the migrating terminus. Indeed, cyclic acetals **8** also undergo thermal cleavage reaction but require higher temperatures.

In these cases, the cleavage reaction does not involve a fragmentation, but an isomerization of the acetals **8** to yield the corresponding acyclic esters **10**. Therefore the pressure-increase technique we employed for acyclic acetals to follow the kinetics was not adequate.[3b]

These problems prompted us to undertake some experiments related more specifically with the hydrogen transfer itself, using both a 2-proteo- and a 2-deuterio-5-alkylidenedioxane **8**.

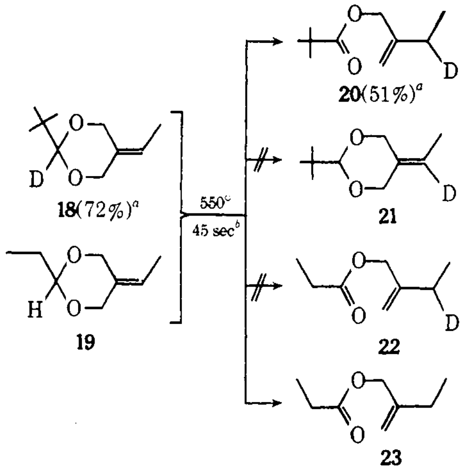
Synthesis of 2-*tert*-Butyl-5-ethylidenedioxane-2-*d*. The general procedure for the synthesis of 5-alkylidenedioxanes has been described by us previously.[7] In the present case, the key intermediate was pivalaldehyde-*1-d* (**15**), which was prepared by a sequence of deuterium incorporation steps as shown in Scheme I; the processes and the conditions were those of Seebach for the synthesis of benzaldehyde-*1-d*.[8] Condensation of **15** with diol **16** gave acetal **17**, which was pyrolyzed at such a temperature that the retro-Diels-Alder reaction of **17** took place without causing the rearrangement of dioxane **18**. The deuterium incorporation as measured by means of a nmr integration was 72% both in aldehyde **15** and dioxane **18**.

Scheme I



Rearrangement of 5-Alkylidenedioxanes. First of all, our aim was to prove the intramolecular [1,5] shift of the hydrogen atom at the C-2 position in the isomerization of **8** to **10**. For this purpose, we have chosen to examine the possibility of an isotope crossover in the thermolysis of a 1:1 mixture of deuterated dioxane **18** and an undeuterated analog, 2-ethyl-5-ethylidene-1,3-dioxane (**19**). The choice of dioxanes **18** and **19** is dictated by the requirement that the rates of isomerization of both compounds are comparable so that such an experiment is meaningful and valid. In Scheme II, conditions of the pyrolysis and results are summarized, from which a number of conclusions can be obtained.

Scheme II



[a] Deuterium incorporation in parentheses. [b] Conversion of the dioxanes: 75 ± 5%.

(1) The undeuterated dioxane **19** isomerizes exclusively to (2-methylene)butylpropionic acid ester (**23**) in which no deuterium is incorporated as shown by the nmr spectrum; in other words, compound **22** has not been found in the reaction mixtures.

(2) The deuterium in the products is found exclusively in the pivalate **20** and is specifically located at the C-3 position in the alkyl chain. Together with the above fact, the results indicate that each dioxane has undergone an intramolecular [1,5] hydrogen migration.

(3) The recovered dioxane **18** shows an nmr pattern for the ethylidene group identical with that of the starting material; no dioxane **21** has been detected in the reaction mixture. This fact suggests that the rearrangement is irreversible. This conclusion is to be expected since the $\Delta\Delta H°_{298}$ (dioxane **18**-ester **20**) is calculated[9] to be ~16 kcal/mol in favor of the ester, which, furthermore, possesses a higher entropy factor at 550°.

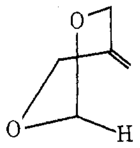
(4) The deuterium content of ester **20** amounts to only 51% while the percentage of deuterium in the recovered dioxane **18** rises to 94%. This enrichment reveals a significant first-order deuterium isotopic effect which is in agreement with the conclusion obtained so far.

Deuterium Kinetic Isotopic Effect. In order to estimate the deuterium kinetic isotopic effect in the rearrangement, dioxane **18** with lower deuterium contents was pyrolyzed alone in the gas phase. From the experimental results, the deuterium kinetic isotopic effects k_H/k_D were calculated; they are summarized in Table I. The scatter in these values arises mainly from uncertainty in the conversion of the ratio of **18**. The observed value of 3 ± 1 at 510° for k_H/k_D is in the range reported for other [1,5] hydrogen migrations having a highly symmetrical transition state,[10,11,12] although the large uncertainty precludes definite conclusions about the geometry of the transition state for the pyrolysis of **18**.

Conclusion

In summary, our observations on the thermal rearrangement of dioxanes of type **8** have shown that the reaction is intramolecular (lack of crossover), that it involves a specific [1,5] hydrogen shift with double-bond migration,[5,6] and that the hydrogen shift occurs in the slow reaction step.

These experimental data are characteristic for a concerted [1,5] sigmatropic reaction. Recent mechanistic proposals for the retro-ene reaction[13] have underlined the linear (coaxial) relationship of the hydrogen and the atoms between which it is transferred in the transition state. For 5-alkylidene-1,3-dioxanes, a bicyclic transition state **24**, arising from a boat conformation **9**, would be required. Such a structure is highly strained, but, in view of the large activation barrier involved in the reaction, the geometry of **24** may be attainable.



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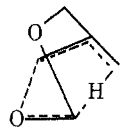

24

Experimental Section

The fractional distillation and the preparative glc techniques used are the same as earlier.[2] The infrared spectra were taken as liquid films. Nmr spectra were taken at 60 MHz in carbon tetrachloride with TMS as internal standard.

2-*tert*-**Butyl-1,3-dithiane (12).** The compound was prepared according to Seebach's general procedure.[8] Starting from 162 g (1.5 mol) of 1,3-propanedithiol and 129 g (1.5 mol) of pivalaldehyde there was obtained 167 g (64%) of distilled dithiane **12**: bp 115° (14 mm); $n^{40}\mathrm{D}$ 1.5305. The colorless liquid crystallized on standing: mp 37.5°; ir 2980, 2910, 1500, 1350, and 900 cm^{-1}; nmr 1 H singlet at δ 8.08, 9 H singlet at δ 2.27.

2-*tert*-**Butyl-1,3-dithiane-***2-d* **(14).** was prepared according to Seebach's general procedure.[8] Starting from 156 g (0.89 mol) of **12**, 144 g (92%) of **14** was obtained, ir new bands at 1015, 1030, and 742 cm^{-1}. The nmr integration of the singlet at δ 8.08, when compared to the other signals, shows an isotopic mixture containing 72% of 2-*tert*-butyl-1,3-dithiane-*2-d* (**14**).

Pivalaldehyde-*1-d* **(15).** In a three-necked reaction vessel (thermometer, stirrer, and condenser), 144 g (0.82 mol) of dithiane **14**, 150 ml of water, 1200 ml of dioxane, 445 g of mercuric chloride, and 161 g of mercuric oxide[8] were heated to gentle boiling under nitrogen. The orange slurry turned white and the solution became green. After 4 hr the condenser was replaced by a distillation column. The distilling pivalaldehyde **15** was collected in a trap cooled to −5°. The collected mixture (76 g) contained the aldehyde and small amounts of water and dioxane. The distillate was washed twice with water and dried over calcium chloride to give aldehyde **15** (64 g), which still contained a trace of dioxane. The overall yield calculated from starting pivalaldehyde was 49.5%. The ir spectrum of **15** was similar to that of undeuterated aldehyde with additional bands at 2140, 2100, 1255, 1120, 1060, and 855 cm^{-1}. In the nmr spectrum, the integration of proton H-1 at δ 9.4 was compared to that of the *tert*-butyl protons at δ 1.17 and showed an isotopic content of 70–75% of pivalaldehyde-*1-d* (**15**).

2-*tert*-**Butyl-5-ethylidene-1,3-dioxane-***2-d* **(18).** The acetal formation and the procedure of retrodienic pyrolysis have been described previously.[7] The nmr spectra of the undeuterated species **18** have also been described.[4] Integrations of the signals between δ 3.75 and 4.18 (3 protons $\mathrm{OCH_2}$ plus H-2 protons) and the signal of the singlet at δ 0.92 (9 *tert*-butyl protons) showed that the isotopic mixture **18** contains 72% of dioxane-*2-d*.

Thermal Isomerization of Dioxane 18. The pyrolysis technique, the synthesis, and data of compounds **19** and **23** have been described elsewhere.[2] The isotopic mixtures **18** with different deuterium contents were obtained by mixing the deuterated **18** (deuterium content 72%) with undeuterated **18**. The conversions were calculated after calibration of the glc chromatograms with pure samples of dioxanes and esters on two different columns (SE-30 and Reoplex on Chromosorb W-HMDS). The isotopic effect has been calculated as follows.

Let $a_s\mathrm{H}$, $a_r\mathrm{H}$ and $a_s\mathrm{D}$, $a_r\mathrm{D}$ be the concentrations of the starting and recovered proteo and deuterio dioxanes, respectively. The measured total conversion X relates these quantities as follows.

$$a_r\mathrm{H} + a_r\mathrm{D} = (1 - X)(a_s\mathrm{H} + a_s\mathrm{D}) \qquad (1)$$

The kinetic isotope effect is given by eq 2.[14]

$$\frac{k_\mathrm{H}}{k_\mathrm{D}} = \frac{\log(a_r\mathrm{H}/a_s\mathrm{H})}{\log(a_r\mathrm{D}/a_s\mathrm{D})} \qquad (2)$$

The measured deuterium contents $\mathrm{D_s}$ and $\mathrm{D_r}$ (Table I) are related to the ratio of the starting and recovered deuterio and proteo dioxanes in the following way.

$$\frac{\mathrm{D_s}}{100 - \mathrm{D_s}} = \frac{a_s\mathrm{D}}{a_s\mathrm{H}} = i_s \qquad (3)$$

$$\frac{\mathrm{D_r}}{100 - \mathrm{D_r}} = \frac{a_r\mathrm{D}}{a_r\mathrm{H}} = i_r \qquad (4)$$

By replacing the parameters in eq 1 with their equivalent values in eq 3 and 4, the following relations are obtained.

$$\frac{a_r\mathrm{H}}{a_s\mathrm{H}} = (1 - X)\,\frac{1 + i_s}{1 + i_r} \qquad (5)$$

$$\frac{a_r\mathrm{D}}{a_s\mathrm{D}} = (1 - X)\,\frac{1 + 1/i_s}{1 + 1/i_r} \qquad (6)$$

Thus $k_\mathrm{H}/k_\mathrm{D}$ in eq 2 can be computed from the experimental data X, $\mathrm{D_s}$, and $\mathrm{D_r}$.

2-Methylenebutyl-*3-d***-pivalic Acid Ester (20).** The ir was similar to that of the undeuterated butyl ester with additional bands at 2300, 2100, 1015, and 815 cm^{-1}. The deuterium amount is calculated by nmr; the integration of the $\mathrm{CH_2}$ quartet of the butyl group at δ 2.1 is compared to that of the $\mathrm{OCH_2}$ at δ 4.48 or the methylene at δ 4.92.

Acknowledgment. We thank Professor Y. L. Chow for many constructive discussions.

Registry No. 12, 6007-21-2; **14,** 49810-98-2; **15,** 41162-98-5; **18,** 49811-00-9; 1,3-propanedithiol, 109-80-8; pivalaldehyde, 630-19-3.

References and Notes

(1) Laboratoire Associé au Centre National de la Recherche Scientifique, No. 135.

(2) F. Mutterer, J. M. Morgen, J. M. Biedermann, F. Weiss, and J. P. Fleury, *Tetrahedron*, **26**, 477 (1970).

(3) (a) H. M. R. Hoffmann, *Angew. Chem.*, **81**, 597 (1969); (b) F. Mutterer, P. Baumgartner, and J. P. Fleury, *Bull. Soc. Chim. Fr.*, 1528 (1970).

(4) P. DeSaulles and J. P. Fleury, *Org. Magn. Resonance*, **2**, 245 (1970).

(5) C. K. Ingold, "Structure and Mechanism in Organic Chemistry," Cornell University Press, Ithaca, N. Y., 1953, p 599.

(6) P. de Mayo, "Molecular Rearrangements," Vol. I, Interscience New York, N. Y., 1963, p 30.

(7) F. Mutterer, J. M. Morgen, J. M. Biedermann, J. P. Fleury, and F. Weiss *Bull. Soc. Chim. Fr.*, 4478 (1969).

(8) D. Seebach, B. W. Erickson, and G. Singh, *J. Org. Chem.*, **31**, 4304 (1966).

(9) D. R. Stall, E. F. Westrune, and G. C. Sinke, "The Chemical Thermodynamics of Organic Compounds," Wiley, New York, N. Y., 1969.

(10) W. R. Roth and J. Konig, *Justus Liebigs Ann. Chem.*, **699**, 24 (1966).

(11) H. Kloosterziel and A. P. ter Borg, *Recl. Trav. Chim. Pays-Bas*, **84**, 1305 (1965).

(12) C. H. de Puy and R. W. King, *Chem. Rev.*, **60**, 431 (1960).

(13) H. Kwart and J. Slutsky, *Chem. Commun.*, 1182 (1972).

(14) L. Melander, "Isotope Effects on Reaction Rates," Ronald Press, New York, N. Y., 1960.