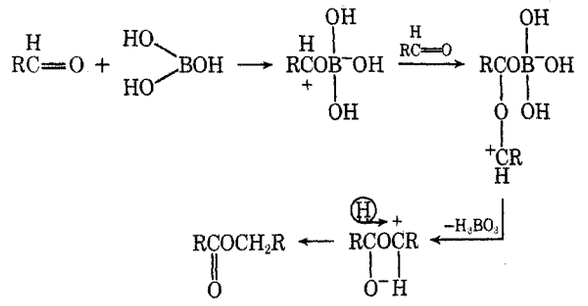
TABLE I[a]

$2RCHO \longrightarrow RCO_2CH_2R$

R	Registry no. (RCHO)	Mol	Conversion, %	Yield,[b] %	Bp, °C (mm)	Registry no. (RCO_2CH_2R)
H	50-00-0	5.83	100	77	32–33	107-31-3
$(CH_3)_2CH-$	78-84-2	3.13	74	72	144–145	97-85-8
$C_4H_9C(C_2H_5)H-$	123-05-7	1.95	52	90	113–115 (1.0)	7425-14-1
c-C_6H_9[d]	100-50-5	2.05	91	60	115–117 (0.5)	2611-00-9
C_6H_5	100-52-7	2.36	34	90	137–140 (0.2)	120-51-4
n-C_3H_7	123-72-8	3.54	82	12[c]	60–65 (12.0)	109-21-7

[a] Reactions were carried out for 6 hr at 250° using 20 g (0.32 mol) of boric acid in 200 ml of heptane or cyclohexane diluent. [b] Based on reacted aldehyde. [c] The total product contained 83% of 2-ethyl-2-hexenal and 17% of n-butyl n-butyrate. [d] 1-Cyclohex-3-enyl.

boron atom. Upon coordination with a carbonyl group and rehybridization from sp^2 to sp^3 the boron atom would become tetracovalent and assume a formal negative charge.[5]



Addition of a second mole of aldehyde to the charged intermediate, loss of boric acid, and intramolecular hydride transfer would occur as depicted. This scheme would account for the observation that fused boric oxide is an inferior catalyst, since formation of a charged tetracovalent intermediate would become much more difficult. The decrease in rate of reaction using the relatively basic tetrahydrofuran solvent and complete inhibition by added water would be expected, since both would compete with the carbonyl group for coordination with the boron atom.

Experimental Section[6]

Disproportionation of Aldehydes over Boric Acid.—A 1-l. stainless steel Magnedrive[7] autoclave was charged with 20 g (0.32 mol) of boric acid, 200 ml of solvent, and the quantity of aldehyde shown in Table I. The autoclave was sealed, flushed with nitrogen, and heated at 250°. After cooling, the product was removed, filtered, and fractionated through a 0.75 × 36 in. helices packed column. The product esters were identified by comparison of their infrared and nmr spectra with those of authentic samples.

Boric Acid Catalyzed Reaction of n-Butyraldehyde.—A mixture of 255 g (3.54 mol) of n-butyraldehyde and 20 g of boric acid in 200 ml of heptane was heated for 6 hr at 250°. After filtration and fractionation there was obtained 45.9 g of unreacted n-butyraldehyde and 164.3 g of material, bp 60–65° (12 mm), which by glpc analysis (10 ft × 0.25 in. Carbowax 20M on Chromosorb P, 150°) was found to consist of 83% 2-ethyl-2-hexenal and 17% n-butyl n-butyrate.

Reaction of Benzaldehyde with n-Butyl Borate.—A mixture of 250 g (2.36 mol) of benzaldehyde, 21 g (0.091 mol) of freshly distilled n-butyl borate,[8] and 200 ml of dry cyclohexane was heated for 6 hr at 200°. The resulting product was washed with water, then with Na_2CO_3 solution, dried ($MgSO_4$), and filtered, and the cyclohexane was removed. The residue, weighing 257.3 g, was analyzed by glpc on a 10 ft × 0.25 in SE-30 on Chromosorb P column at 175° and was found to contain 9.8% of benzyl alcohol, 80.4% of benzaldehyde, and 9.1% of α-ethylcinnamaldehyde. Benzyl alcohol and α-ethylcinnamaldehyde were separated by preparative glpc and identified by comparison of infrared and nmr spectra with authentic samples.

Registry No.—Boric acid, 10043-35-3; 2-ethyl-2-hexenal, 645-62-5; n-butyl borate, 688-74-4.

(5) H. Steinberg, "Organoboron Chemistry," Vol. I, Wiley, New York, N. Y., 1964, p 31.

(6) The aldehydes used were the best commercial grades and were purified by fractionation through a 36-in. helices packed column. Heptane and cyclohexane were Phillips Petroleum Co. Pure Grade materials and were used as received. Boric acid and fused boric oxide were obtained from Mallinckrodt.

(7) Autoclave Engineers, Inc., Erie, Pa.

(8) J. R. Johnson and S. W. Tompkins, "Organic Syntheses," Collect. Vol. II, Wiley, New York, N. Y., 1943, p 106.

Communications

See Editorial, J. Org. Chem., 38, No. 19, 4A (1972)

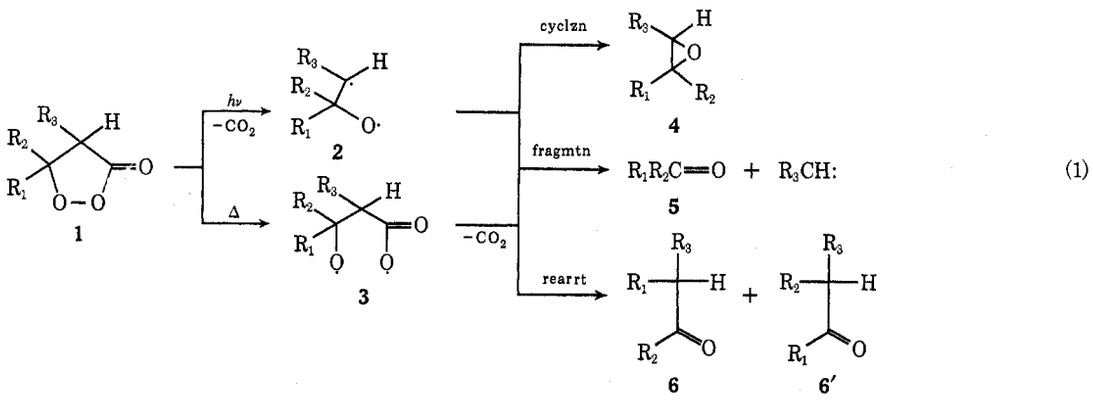
1,3 Diradicals *via* Thermolysis of 1,2-Dioxolanes[1]

Summary: Stereochemical and kinetic results suggest direct deketonation of 1,2-dioxacyclopentanes on thermal activation affording 1-oxatrimethylene, which suffers a novel ring expansion.

Sir: From stereolabeling experiments[2] we rationalized that 1,2-dioxolan-3-ones **1** photodecarboxylate (eq 1) directly into the 1-oxatrimethylene diradical **2**, which serves as precursor to epoxide **4**, fragmentation ketone **5**, and the pair of rearrangement ketones **6** ($\sim R_1$) and **6′** ($\sim R_2$). However, in the thermal decomposition of **1** (eq 1), stereolabeling[3,4] and kinetic[5] experiments suggest that the 1,5-dioxa-2-oxopentamethylene diradical **3**

(1) Paper XXVII in the Cyclic Peroxide Series. For previous paper, *cf.* W. Adam and H. C. Steinmetzer, *Angew. Chem.*, **84**, 590 (1972); *Angew. Chem., Int. Ed. Engl.*, **11**, 540 (1972).

(2) W. Adam and G. Santiago Aponte, *J. Amer. Chem. Soc.*, **93**, 4300 (1971).



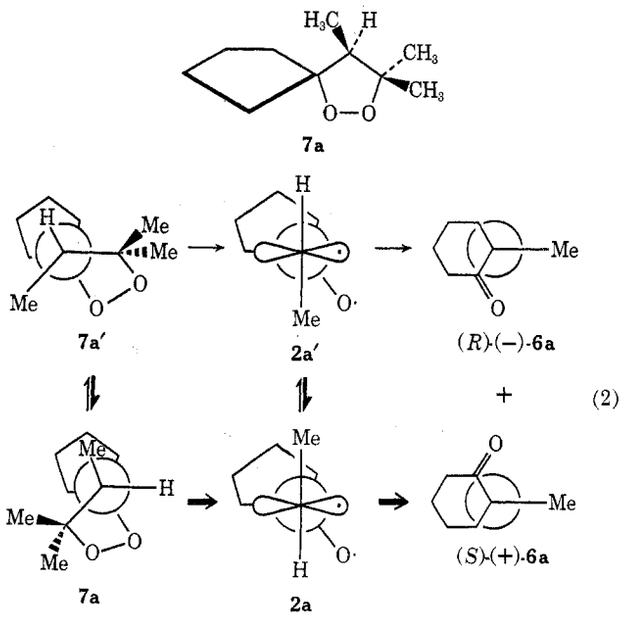
(1)

intervenes, which suffers principally stereospecific rearrangement into **6** and **6′**. Since 1,2-dioxolanes **7** deketonate thermally[6] and photochemically[7] into the same types of products, it was of mechanistic interest to examine the stereochemistry and kinetics of this deketonation process, and presently we wish to report our results.

For the stereochemical study we employed (*S*)-(+)-3,3,4-trimethyl-1,2-dioxaspiro[4.4]nonane (**7a**), bp 57–58° (0.9 mm), $\alpha^{20}D$ +1.58° (*c* 4.47, CCl_4), which was prepared *via* a stereospecific route starting with 88.9% optically pure (*R*)-(−)-*n*-butyl lactate, $\alpha^{20}D$ −11.9° (neat) [lit.[8] $\alpha^{20}D$ +13.4° (neat)]. First, double Grignard addition of 1,4-dibromobutane afforded (*R*)-(+)-1-(1-hydroxycyclopentyl)ethanol, bp 84–85° (0.7 mm), $\alpha^{25}D$ +0.6° (neat). Treatment of this 1,2-diol with benzenesulfonyl chloride in pyridine, followed by sodium hydride in THF,[2] gave (*S*)-(+)-2-methyl-1-oxaspiro[2.4]heptane, bp 74–75° (86 mm), $\alpha^{25}D$ +14.9° (*c* 3.44, CCl_4). Reaction of this epoxide with 2-lithio-2-methyl-1,3-dithiane in THF at −30° and careful hydrolysis with $HgCl_2/HgO$ in aqueous methanol[9] led to (*R*)-(−)-3-(1-hydroxycyclopentyl)-2-butanone, bp 77–78° (1.3 mm), $\alpha^{25}D$ −24.4° (*c* 4.64, CCl_4). Addition of this β-keto alcohol to excess methylmagnesium bromide in ether produced (*S*)-(−)-3-(1-hydroxycyclopentyl)-2-methylbutan-2-ol, mp 86–87°, $\alpha^{20}D$ −22.1° (*c* 9.77, CCl_4), which was cyclized into the desired (*S*)-(+)-**7a** with 98% H_2O_2 (*CAUTION!*). As a control, (*S*)-(+)-**7a** was reduced catalytically over Pd/C back to the (*S*)-(−)-diol in over 90% yield, mp 86–87°, $\alpha^{20}D$ −22.2° (*c* 1.82, CCl_4), and therefore the 1,2-dioxolane **7a** is assumed to be 88.9% optically pure (*S*)-(+) isomer.[10]

Thermolysis of (*S*)-(+)-**7a** in benzene at 170° for 17 hr and collection by glpc[11] afforded (*S*)-(+)-2-methylcyclohexanone (**6a**), $\alpha^{25}D$ +0.29 ± 0.07° (*c* 1.69, C_6H_6), which corresponds to $\alpha^{25}D$ +0.33 ± 0.08° after correction for 88.9% optical purity of (*S*)-(+)-**7a**. Authentic (*S*)-(+)-**6a** of 23.3% optical purity,[12] $\alpha^{25}D$ +0.91° (*c* 1.43, C_6H_6), was prepared by kinetic resolution of **6a** with di-3-pinanylborane[13] and collected by glpc.[11] Control experiments indicated that the rearrangement ketone (*S*)-(+)-**6a** did not racemize when submitted to the thermolysis conditions in the presence of 1,2-dioxolane **7a**, nor on glpc collection.[11] Thus, (*S*)-(+)-**6a** was formed with 8.4 ± 2.0% net retention of configuration[12] directly in the thermolysis of (*S*)-(+)-**7a** and was not racemized in secondary reactions.

To accommodate this stereochemical result of the novel ring expansion in the thermodeketonation of **7a**, we propose that diradical **2a** is the precursor to **6a** (eq 2). Diradical **2a** suffers extensive racemization either by bond rotation between rotamers **2a′** and **2a** or possibly through conformational effects dictated already in the 1,2-dioxolane rotamers **7a** and **7a′**. In contrast, it should be recalled that 1,2-dioxolan-3-ones **1** undergo thermodecarboxylation with quantitative inversion at the 4 position (migration terminus), which obliged us to propose that the 1,5 diradical **2** and not the 1,3 diradical



(2)

(3) W. Adam, Y. M. Cheng, C. W. Wilkerson, and W. A. Zaidi, *J. Amer. Chem. Soc.*, **91**, 2111 (1969).

(4) W. Adam and C. Wilkerson, *J. Chem. Soc., Chem. Commun.*, 1509 (1971)

(5) W. Adam and Y. M. Cheng, *J. Amer. Chem. Soc.*, **91**, 2009 (1969).

(6) W. Adam and N. Durán, *J. Chem. Soc. Chem. Commun.*, 279 (1972).

(7) W. Adam and N. Durán, *Tetrahedron Lett.*, 1357 (1972).

(8) C. F. Wood, J. E. Such, and F. Scarf, *J. Chem. Soc.*, 1928 (1936).

(9) D. Seebach, University of Giessen, private communication; D. Seebach, *Synthesis*, **1**, 35 (1969).

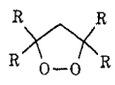
(10) In this assignment it is assumed that no partial racemization occurred during any of the steps of the stereospecific preparation of **7a**, since in ref 2 we showed that such an epoxide synthesis takes place with quantitative inversion, while in ref 9 it was shown that epoxide opening by the Seebach-Corey reagent also occurs with quantitative inversion.

(11) For the glpc collection at 20 ft × 0.25 in. copper column packed with 20% FFAP on 80–100 mesh Chromasorb P was used, operated at column, detector, and injector temperatures of 155, 160, and 165°, respectively, and a helium flow of 60 ml/min.

(12) 2-Methylcyclohexanone of 100% optical purity has $\alpha^{25}D$ +12.01° (neat) as reported by D. Mea-Jocheet and A. Horeau, *Bull. Soc. Chim. Fr.*, 4571 (1962). Material of 23.3% optical purity, prepared *via* kinetic resolution, has $\alpha^{25}D$ +2.80° (neat), +2.50° (*c* 3.5, EtOH), and +0.91° (*c* 1.46, C_6H_6).

(13) J. D. Morton and H. S. Mosher, "Asymmetric Organic Reactions," Prentice-Hall, Inc., Englewood Cliffs, N. J., 1971.

TABLE I
KINETIC DATA FOR THE THERMOLYSIS OF 1,2-DIOXOLANES IN BENZENE[a]



7

	T, (°K)	$k \times 10^5$ (sec^{-1})[b]	$\Delta H^{\pm}$ (kcal/mol)	$\Delta S^{\pm}$ (gibbs/mol)	$\Delta G^{\pm}$ at 500° K (kcal/mol)
	463.2	0.553 ± 0.014			
7b (R = Me)	473.2	1.17 ± 0.06	27.0 ± 0.3	−24.8 ± 0.7	34.4 ± 0.3
	491.2	3.20 ± 0.15			
	463.2	9.04 ± 0.5			
7c (R = Ph)	472.7	15.0 ± 0.6	21.7 ± 0.5	−30.8 ± 2.2	37.1 ± 0.5
	492.2	39.0 ± 2.8			

[a] Error limits have been assessed by least-squares analysis of the rate data employing an IBM computer. [b] Averaged over several runs!

3 served as precursor to rearrangement ketones **6** (eq 1).[3-5]

Of course, this stereochemical result cannot decide whether the 1,3 diradical **2a** is formed from **7a** *via* direct deketonation or whether first simply the peroxide bond in **7a** cleaves to give a 1,5 diradical similar to **3**, which after loss of ketone results in the 1,3 diradical **2a**. For this purpose we examined the kinetics of the thermolysis of 3,3,5,5-tetramethyl- and 3,3,5,5-tetraphenyl-1,2-dioxolanes **7b** and **7c**, respectively, to see whether $\Delta H^{\pm}$ and $\Delta S^{\pm}$ exhibit a dependence on structure.[14] The appearance of carbonyl product was monitored by ir and in all runs good first-order rates were obtained for at least two half-lives. The data is summarized in Table I. Furthermore, it was shown that the rate of acetone production from **7b** is identical within experimental error in C_6H_6 and CH_3CN. No doubt a homolytic fission of the peroxide bond is involved and a structure-reactivity dependence is clearly evident; *i.e.*, benzophenone as leaving group in **7c** helps to lower the activation enthalpy compared to acetone in **7b**, but a considerable price must be paid in the activation entropy, implying a two-bond homolysis and thus direct ketone expulsion (eq 2). However, the activation parameters themselves are rather unexpected, particularly the very negative $\Delta S^{\pm}$ values, and need further comment.

For comparison, the values for di-*tert*-butyl peroxide are $\Delta H^{\pm}$ = 37.8 kcal/mol, $\Delta S^{\pm}$ = +13.8 gibbs/mol, and $\Delta G^{\pm}$ (500°K) = 31 kcal/mol,[15] revealing that the cyclic analog **7b** is by a factor $\sim 3 \times 10^3$ more stable toward thermolysis than di-*tert*-butyl peroxide. The significantly lower $\Delta H^{\pm}$ for the cyclic peroxide **7b** compared with the acyclic analog is not unreasonable since conformational constraint on the oxygen lone pairs is expected to yield a weaker peroxide bond.[16] However, the $\Delta S^{\pm}$ values are without parallel for unimolecular decompositions and certainly cannot be rationalized in terms of two-bond homolysis alone. Excepting the possibility of reduced transmission coefficients in the Eyring equation, possible factors contributing to these unusual $\Delta S^{\pm}$ values might be (a) a high rate of reclosure of 1,5 diradicals, implying that its deketonation is rate determining, (b) a need of selective twisting skeletal deformations in unzipping the ketone leaving group *via* two-bond homolysis in **7**, and (c) an unusually low rotational entropy for the 1-oxatrimethylene diradicals. In the absence of additionally needed experimental data, at this moment we cannot make any commitments as to which of the above factors contributes predominantly to the very negative activation entropies in the deketonation of 1,2-dioxolanes **7**.

(14) P. D. Bartlett and R. Hiatt, *J. Amer. Chem. Soc.*, **80**, 1398 (1958).
(15) W. A. Pryor, "Free Radicals," McGraw-Hill, New York, N. Y., 1966, p 51.
(16) C. W. Gillies and R. L. Kuczkowski, *J. Amer. Chem. Soc.*, **94**, 6337 (1972).

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(17) Alfred P. Sloan Foundation Fellow, 1968–1972.
(18) On study leave from the Catholic University of Valparaiso, Chile.

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Functionalization of Penicillins at Carbon 6 *via* *N*-Acylimines. 6-Hydroxypenicillin. Substituted Penicillins and Cephalosporins. VIII[1]

Summary: Introduction of 6α-hydroxy, methoxy, benzyloxy, and formyloxy into penicillin G benzyl ester (**2e**) has been achieved by the addition of the appropriate hydroxy compound to the *N*-acylimine **6**, prepared from **2e** by halogenation and elimination.

Sir: The finding that a 6(7)α-methoxy group confers β-lactamase stability on penicillins and cephalosporins[2] has stimulated a search for synthetic methods of introducing this and other groups. Particularly sought was 6α-hydroxypenicillin (**1a**) since its antimicrobial activity might be different from that of 6α-methoxypenicillin (**1b**), whose potency is lower than that of the parent, penicillin G (**1e**).[3]

Substituents of many kinds can be introduced into penicillins and cephalosporins at C-6(7) by the addition of nucleophiles to the geminal bromo azide **3**.[3] Similarly, electrophilic reagents react at that position with a carbanion which is stabilized by being adjacent to both the β-lactam carbonyl and an azomethine double bond built on the C-6(7)-amino group.[4] Thus, compounds **4**

(1) Paper VII: L. D. Cama and B. G. Christensen, *Tetrahedron Lett.*, submitted for publication.
(2) E. O. Stapley, M. Jackson, S. Hernandez, S. B. Zimmerman, S. A. Currie, S. Mochales, J. M. Mata, H. B. Woodruff, and D. Hendlin, *Antimicrob. Ag. Chemother.*, **2**, 122 (1972); T. W. Miller, R. T. Goegelman, R. G. Weston, I. Putter, and F. F. Wolf, *ibid.*, 132 (1972); A. K. Miller, E. Celozzi, B. A. Pelak, E. O. Stapley, and D. Hendlin, *ibid.*, 281 (1972).
(3) L. D. Cama, W. J. Leanza, T. R. Beattie, and B. G. Christensen, *J. Amer. Chem. Soc.*, **94**, 1408 (1972).
(4) R. Reiner and P. Zeller, *Helv. Chim. Acta.*, **51**, 1905 (1968); E. H. W. Böhme, H. E. Applegate, B. Toeplitz, J. E. Dolfini, and J. Z. Gougoutas, *J. Amer. Chem. Soc.*, **93**, 4324 (1971); R. A. Firestone, N. Schelechow, D. B. R. Johnston, and B. G. Christensen, *Tetrahedron Lett.*, 375 (1972); W. A. Spitzer, T. Goodson, R. J. Smithey, and I. G. Wright, *Chem. Commun.* 1139 (1972); D. B. R. Johnston, S. M. Schmitt, R. A. Firestone, and B. G. Christensen, *Tetrahedron Lett.*, 4917 (1972).