(q), 26.8 (q), 17.9 (q), 17.6 (t), 17.6 (q); HRMS obsd m/z 263.1703, $C_{16}H_{25}NS$ requires 263.1709.

Single-Crystal X-ray Diffraction Analysis of 5. A suitable single crystal was glued to a glass fiber, and preliminary X-ray photographs were taken. Compound **5** had orthorhombic symmetry with a = 9.543 (2), b = 10.371 (2), and c = 15.373 (3) Å. Systematic absences, a calculated density, and the compound's optical activity were uniquely accommodated by space group $P2_12_12_1$ with one molecule of composition $C_{16}H_{25}NS$ forming the asymmetric unit. All unique diffraction maxima with $2\theta \leq 114°$ were collected on a computer-controlled four-circle diffractometer using Cu Kα radiation and variable speed 1° ω-scans. Of the 1206 unique reflections collected this way, 948 (79%) were judged observed after correction for Lorentz, polarization, and background effects.[11] The structure was phased using direct methods, and the initial maps clearly revealed the heavy atom structure. Hydrogen atoms were located in a ΔF-synthesis after partial refinement of the heavy atoms. Block-diagonal least-squares refinements with anisotropic heavy atoms and fixed isotropic hydrogens have converged to a conventional crystallographic residual of 0.063. Additional crystallographic information is available in the supplementary material.

Acknowledgment. The sponge was collected by Dr. Valerie Paul (University of Guam) and identified by Dr. Rob van Soest. This research was supported by grants from the National Institutes of Health (AI11969 to D.J.F. and CA24487 to J.C.) and the New York State and California (R/MP40) Sea Grant College Programs.

Supplementary Material Available: Tables of atomic coordinates, thermal parameters, interatomic distances, interatomic angles, and torsional angles for 5-isothiocyanatopupukeanane (**5**) (5 pages). Ordering information is given on any current masthead page.

(11) All crystallographic calculations were done on a PRIME 850 computer operated by the Cornell Chemistry Computing Facility. Principal programs employed: Leonowicz, M. E. REDUCE and UNIQUE, data reduction programs, Cornell University, 1978. Main, P.; Hull, S. E.; Lessinger, L.; Germain, G.; Declercq, J. P.; Woolfson, M. M. MULTAN 78, MULTAN 80, and RANTAN 80, systems of computer programs for the automatic solution of crystal structures from X-ray diffraction data (locally modified to perform all Fourier calculations including Patterson syntheses), University of York, England, 1979 and 1980. Beurskens, P. T.; et al. DIRDIF, University of Nijmegen, The Netherlands, 1981. Gilmore, C. J. MITHRIL, an automatic solution package, University of Glasgow, Scotland, 1983. Hirotsu, K. K.; Arnold, E. BLS78A, an anisotropic block-diagonal least-squares refinement, Cornell University, 1980. Motherwell, W. D. S. PLUTO78, a crystallographic illustration program, Cambridge Data Centre, 1978. Hirotsu, K. BOND, a program to calculate molecular parameters and prepare tables, Cornell University, 1978.

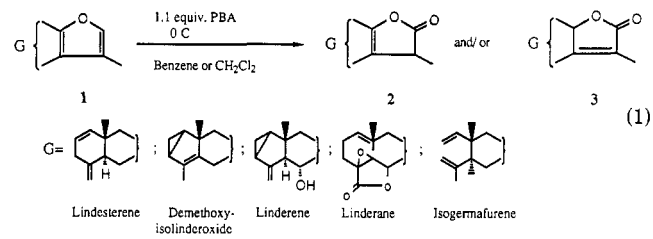
Effect of Acid on the Peracid Oxidations of 3-Methyltetrahydrobenzofuran

K. P. Manfredi and P. W. Jennings*

Gaines Hall Laboratories, Department of Chemistry, Montana State University, Bozeman, Montana 59717

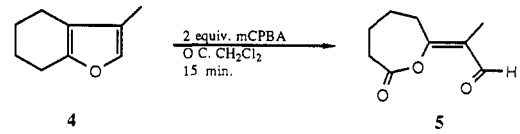
Received February 23, 1989

Prior to recent work in this laboratory on the peracid oxidations of tetrahydrobenzofuran derivatives, Takeda reported on the oxidations of lindesterene,[1] demethoxyisolinderoxide,[2] isogermafurene,[3] linderene,[3] and linderane,[4] which are shown in a generic type of reaction sequence as eq 1. It appears from this literature that the unconjugated γ-lactone is the primary product while the conjugated isomer results from subsequent isomerization during isolation.



(1)

In 1981, we reported[5] on the *m*-chloroperbenzoic acid (mCPBA) oxidation of a simpler system, 3-methyltetrahydrobenzofuran **4**, as shown in eq 2. In this case and with

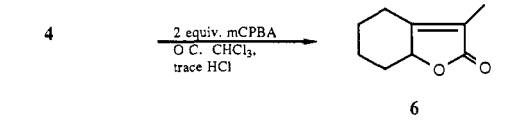


(2)

other derivatives, 2 equiv of peracid were required,[6] and the sole product was the ϵ-lactone aldehyde **5**. The same result was observed with perbenzoic acid (PBA) and with *p*-nitroperbenzoic acid (pNPBA).[7] Moreover, with use of the conditions reported by Takeda,[1] **5** was still the only product *observed*.[7] In this note, we wish to report the resolution to this apparent dichotomy.

Results

Inadvertantly, in our laboratory substrate **4** was reacted with impure mCPBA that apparently contained a small but unspecified amount of HCl. In this experiment, we obtained butenolide **6** as shown in eq 3. Repetition of the



(3)

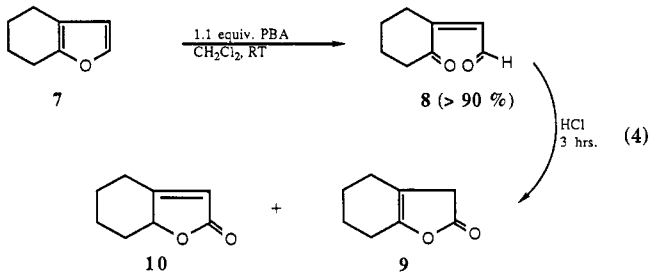
experiment with a trace of concentrated aqueous HCl led to the same result. In another experiment, **4** was dissolved in ethanol-free $CHCl_3$, and a trace of aqueous HCl added. The light pink color that developed in the reaction mixture dissipated quickly when 1.4 equiv of PBA were added. The γ-lactone product **6** was obtained in better than 90% yield. The concentration of PBA was determined not to be a factor since both 2 and 1.4 equiv gave the same product in the same concentration.

Further investigation revealed that any one of the peracids PBA, mCPBA, or pNPBA gave the γ-lactone product in the presence of catalytic amounts of aqueous HCl. Moreover, the solvent may be CH_2Cl_2, THF, benzene, ether, or $CHCl_3$. Finally, in addition to HCl (aq), H_2SO_4, *p*-TsOH, HOAc, and HCl (g) catalyzed the formation of **6**.

With use of an even simpler substrate **7**, further insight into the pathway of this reaction was obtained (eq 4). In this reaction, **7** was reacted with 1.1 equiv of PBA in *acid-free* CH_2Cl_2 at room temperature, yielding **8**. Subsequent treatment of **8** with a catalytic amount of aqueous

(1) Takeda, K.; Minato, H.; Ishikawa, M.; Miyawaki, M. *Tetrahedron* **1964**, *20*, 2655.
(2) Takeda, K.; Minato, H.; Horibe, I.; Miyawaki, M. *J. Chem. Soc. C* **1967**, 631.
(3) Takeda, K.; Horibe, I.; Minato, H. *J. Chem. Soc. C* **1968**, 569.
(4) Tada, H.; Minato, H.; Takeda, K. *J. Chem. Soc. C* **1971**, 1070.
(5) Gingerich, S. B.; Campbell, W. H.; Bricca, C. E.; Jennings, P. W.; Campana, C. F. *J. Org. Chem.* **1981**, *46*, 2589.
(6) If less than 2 equiv is used, one obtains only **5** and unreacted **4**. One equivalent leads to a 50:50 mixture of **4** and **5**.
(7) Manfredi, K. P. Ph.D. Thesis, Montana State University, 1985.

0022-3263/89/1954-5186$01.50/0



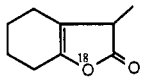
7 8 (> 90 %) (4)

10 9

HCl gave γ-lactones **9** and **10** in a ratio of 70:30, respectively. Finally, oxidation of **7** in the presence of a trace of aqueous HCl gave **9** which, upon standing for 24 h, isomerized completely to **10**.

It is interesting to note that **8** does not readily undergo the Baeyer–Villiger reaction. While this is surprising, we have previously noted that the position of the methyl group dramatically affects the B–V regiochemistry.[8] Thus, its contribution, albeit unknown at this time, is major.

The final endeavor in this investigation involved labeling the furan oxygen to determine additional details regarding the mechanistic sequence. Compound **4** was prepared with 39% ^{18}O label and subsequently reacted with 1.2 equiv of PBA in $CHCl_3$ with a trace of aqueous HCl. The product is shown as structure **11**. By mass spectral measurements, 7% of the label was lost during the reaction. This results will become significant in the mechanistic discussion below.



11

Discussion

Previous work on **4** and similar systems by Gingerich[8] led to the mechanistic sequence shown as Scheme I. With use of similar logic, the acid perturbation could be envisioned to contribute in two ways as shown in Scheme II (paths A and B). Path A is a viable alternative except for the fact that some of the ^{18}O label is lost during the reaction. This small but significant loss appears to necessitate the intermediacy of the dicarbonyl compound (B_2), which could readily exchange the ketonic oxygen in aqueous acid. Further support for the dicarbonyl intermediate is garnered from the oxidation of **7**, which leads to **8** and subsequently closes to the γ-lactone in acid media. It is important to note that this small loss of label does not require that the entire reaction proceed by path B. Thus, it seems reasonable to suggest that there are two alternative mechanisms with different rates. It is also abundantly clear that the presence or absence or H^+ determines the pathway and products of furan oxidations.

Finally, it is important to discuss the origins of trace quantities of acid in the reaction. The most likely source comes from the peracid synthesis and specifically from acidification of the intermediate sodium perbenzoate. If the PBA is not rigorously purified, it will contain trace quantities of acid.

Conclusion

It is now readily apparent that trace quantities of mineral acid in the reaction mixture yields γ-*lactones* from the peracid oxidation of tetrahydrobenzofurans. However, on rigorous purification of the peracid removing any trace of acid, the oxidation proceeds with 2 equiv of peracid to yield ε-*lactone aldehyde* products.

Experimental Section

Proton and carbon NMR experiments were performed on a Bruker WM 250 NMR spectrometer. Multiplicities of carbon resonances were obtained by using a gated decoupled pulse sequence. For the determination of ^{18}O, high-resolution ^{13}C NMR spectroscopy was used with 500-Hz sweep widths. Data were acquired as a 4K data set and transformed as an 8K set. Infrared spectra were obtained on a Beckman IR5A spectrometer calibrated with polystyrene. Nominal mass spectra were obtained on a VG MM16 mass spectrometer operating at 70 eV. Absolute mass measurements were performed on a VG 7070E mass spectrometer at the Montana State University Mass Spectrometry Center.

Analytical gas chromatography was performed on a Varian Model 1700 GC equipped with a flame ionization detector. Columns were 10 ft × $^1/_4$ in. and packed with 3% SE30 on Chromosorb W. Column chromatography was performed using Baker reagent grade silica gel 60–200 mesh. Solvents were purchased from either Fisher or Baker and were purified according to standard laboratory procedures prior to use. Deuterated solvents were purchased from either Wilmad or Stohler, and TMS was added as an internal chemical shift standard.

Synthesis of Substrates. 3-Methyl-4,5,6,7-tetrahydrobenzofuran **4** was synthesized as previously described.[5] The ^{18}O analogue **4*** was synthesized according to the procedure of Gingerich.[10] 4,5,6,7-Tetrahydrobenzofuran (**7**) was synthesized according to the procedure of Wolters.[11]

Synthesis of Perbenzoic Acid. PBA was synthesized according to the procedure of Braun.[9] Benzoyl peroxide (recrystallized two times from $CHCl_3$, 24.75 g, 102 mmol, Eastman) was dissolved in 80 mL of $CHCl_3$ and cooled to 0 °C. A solution of MeO^-Na^+ was prepared by dissolving 2.5 g of sodium in 40 mL of MeOH at −5 °C. The MeO^-Na^+ solution was then added to the benzoyl peroxide, with the precaution that the temperature did not rise above 5 °C. After the addition was complete (0.5 h) the solution was stirred for an additional 5 min. The milky white solution was then extracted with 250 mL of H_2O containing chipped ice. This solution was extracted twice with $CHCl_3$ to remove all traces of methyl benzoate. The sodium perbenzoate in the aqueous phase was acidified by addition of 120 mL of cold (0 °C) 1 N H_2SO_4. The reaction must be kept cold during the acidification to avoid thermal decomposition of the PBA. This solution was then extracted three times with cold $CHCl_3$. The $CHCl_3$ solution was extracted several times with cold water and brine and dried over Na_2SO_4. After recrystallization several times from ether–petroleum ether, the material was stored at −20 °C until needed. Purity of the acid was periodically checked by adding a measured quantity of PBA to a solution of KI in acetic acid–H_2O–$CHCl_3$ and titrating the liberated I_2 with standard $Na_2S_2O_3$.

mCPBA and pNPBA were both of technical grade and purchased from Aldrich. The mCPBA was recrystallized according to the procedure of Schwartz,[12] and its purity assayed by titration with standard $Na_2S_2O_3$.

Oxidation of 4 with PBA, mCPBA, and pNPBA. Addition of 2 equiv of PBA, mCPBA, or pNPBA to a stirred solution of **4** in CH_2Cl_2 produced the previously reported ε-lactone aldehyde **5**. The same experiments were repeated using benzene, THF, ether, and $CHCl_3$ as solvents at 0 and 25 °C. In all cases the ε-lactone aldehyde **5** was the only product.

Oxidation of 4 with PBA and HCl. To a stirred solution of **4** (233 mg) in 20 mL of $CHCl_3$ (ethanol free) at 0 °C was added 10 μL of concentrated HCl (Baker). The solution immediately turned light pink. PBA was then added as a solid (1.4 equiv), and the solution turned light yellow and then colorless within 1

(8) Gingerich, S. B.; Jennings, P. W. *J. Org. Chem.* **1984**, *49*, 1284.

(9) Braun, G. *Org. Synth.* **1944**, *Coll Vol 1* 431.

(10) Jennings, P. W.; Gingerich, S. B. *J. Labelled Compd.* **1983**, *20*, 591.

(11) Scharf, H. D.; Wolters, E. *Angew. Chem., Int. Ed. Engl.* **1976**, *15*, 682.

(12) Schwartz, N. N.; Blumbergs, J. H. *J. Org. Chem.* **1964**, *29*, 1976.

min. The reaction mixture was subsequently washed twice with 10% $Na_2S_2O_3$, twice with 10% $NaHCO_3$, and once with brine and finally dried over K_2CO_3. Removal of solvent at reduced pressure yielded lactone **6** (232 mg, 93%) as a clear colorless oil: ^{13}C NMR ($CDCl_3$) δ 174.8 (s), 162.5 (s), 119.6 (s) 80.1 (d), 34.2 (t), 26.2 (t), 26.2 (t), 22.7 (t), 8.0 (q) ppm; ^1H NMR[13] ($CDCl_3$) δ 4.55 (1 H, m), 2.79 (1 H, m), 2.47 (1 H, m), 2.2–1.8 (3 H, m), 1.78 (3 H, t, J = 1.5 Hz), 1.65–1.0 (3 H, m) ppm; IR[13] (neat) 1760, 1690 cm^{-1}; mass spectrum, m/e (rel intensity) 152 M^+, 123 (61), 95 (100). Anal. (accurate mass) calcd for $C_9H_{12}O_2$: 152.0834. Found 152.0841.

If H_2SO_4 or gaseous HCl was used in conjunction with mCPBA or pNPBA, lactone **6** was the only product produced. Use of acetic acid or pTSOH had similar results, but the yield was lower and other unidentified side products were produced. If the solvent was THF, ether, benzene, or CH_2Cl_2, lactone **6** was the only product produced in the presence of aqueous HCl.

Oxidation of 7 with PBA. To a stirred solution of **7** (150 mg) in 10 mL of CH_2Cl_2 was added 1.1 equiv of PBA (169 mg). The furan was no longer detected after 5 min (GC and TLC), and the reaction was worked up by washing with 10% $Na_2S_2O_3$, 10% $NaHCO_3$, and brine and dried over K_2CO_3. Evaporation of the solvent at reduced pressure yielded the dicarbonyl compound **8** (150 mg 90%) as a light yellow oil: ^{13}C NMR ($CDCl_3$) δ 202.2 (s), 191.9 (d), 157.5 (s), 131.3 (d), 43.4 (t), 36.5 (t), 25.3 (t), 25.3 (t) ppm; ^1H NMR ($CDCl_3$) δ 9.78 (1 H, d, J = 8 Hz), 5.90 (1 H, d, J = 8 Hz), 2.6 (4 H, m), 1.95 (4 H, m) ppm; IR (neat) 1670 (br), 1610 cm^{-1}; mass spectrum, m/e 138 (M^+). 110, 67. Anal. (accurate mass) calcd for $C_8H_{10}O_2$: 138.0681. Found 138.0682.

Oxidation of **7** with either pNPBA or mCPBA also produced **8**. If aqueous acid was added to the reaction prior to addition of peracid, the dicarbonyl compound **8** was still the only product if the reaction was worked up *immediately after the furan was consumed.*

Synthesis of Lactones 9 and 10. To the dicarbonyl compound **8** (560 mg, 4 mmol) in 300 mL of CH_2Cl_2 was added 40 μL of concentrated HCl. After this stirred for 3 h at room temperature, the furan was no longer detectable (GC or TLC). The reaction mixture was then washed with 10% $NaHCO_3$ and brine and dried over K_2CO_3. ^1H NMR spectroscopy showed the products to be a 70:30 mixture of lactones **9** and **10**.

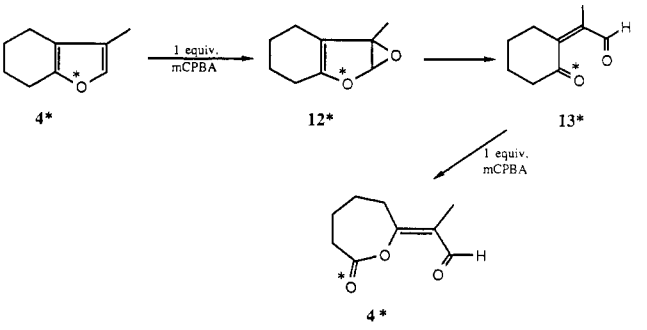
The two lactones were separated by column chromatography on silica gel using an EtOAc–hexane gradient elution system. The β,γ-unsaturated lactone **9** eluted first and was identified based on its spectral properties: ^{13}C NMR ($CDCl_3$) δ 176.5 (s), 150.4 (s), 110.6 (s), 36.0 (t), 22.5 (t), 22.3 (t), 22.3 (t), 22.2 (t) ppm; ^1H NMR ($CDCl_3$) δ 3.1 (2 H, m), 2.25 (2 H, m), 2.1 (2 H, m) 1.8 (4 H, m) ppm; IR (neat) 1792, 1700 cm^{-1}; mass spectrum, m/e (rel intensity) 138 (M^+), 110 (22), 82 (31), 67 (100). Anal. (accurate mass) calcd for $C_8H_{10}O_2$: 138.0681. Found: 138.0681.

The α,β-unsaturated lactone **10** eluted second and was also identified by its spectral properties: ^{13}C NMR ($CDCl_3$) δ 171.9 (s), 151.6 (s), 112.5 (d), 81.4 (d), 34.4 (t), 28.1 (t), 26.6 (t), 22.5 (t) ppm; ^1H NMR ($CDCl_3$) δ 5.7 (1 H, s), 4.65 (1 H, m), 2.95 (1 H, m), 2.65 (1 H, m), 2.3 (2 H, m), 1.95 (2 H, m), 1.35 (2 H, m) ppm; mass spectrum, m/e (rel intensity) 138 (M^+), 109 (100), 81 (30). Anal. (accurate mass) calcd for $C_8H_{10}O_2$: 138.0681. Found: 138.0687.

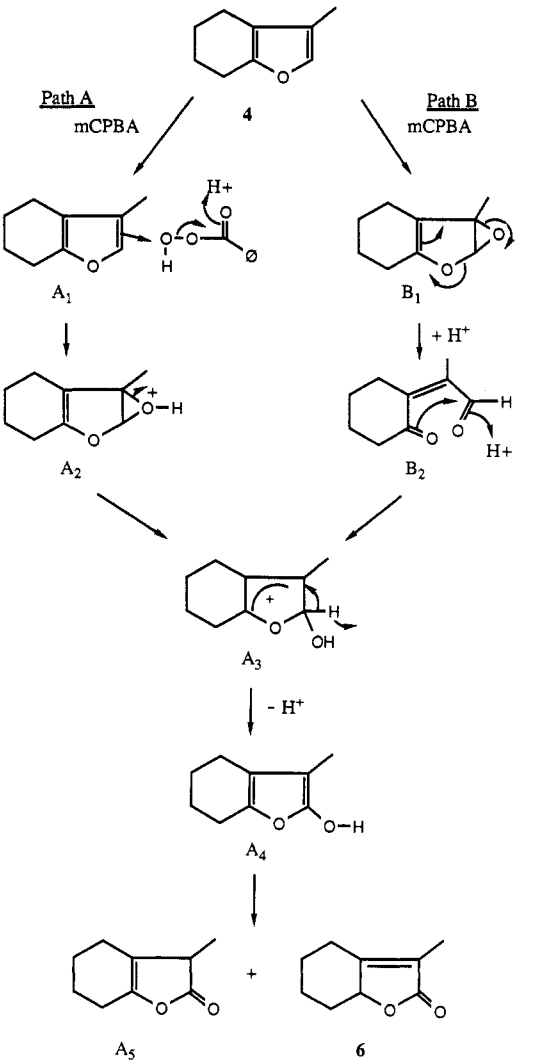
The β,γ-unsaturated lactone **9** readily isomerized to **10** in the GC column. It would also slowly isomerize to **10** in $CDCl_3$ at room temperature.

Oxidation of 4* with PBA and HCl. GCMS analysis of the M^+ and the $(M + 2)^+$ molecular ion (m/z = 150, 152) indicated that there was 39% ^{18}O incorporation in the furan. High-resolution ^{13}C NMR spectroscopy also showed that the furan contained 39% ^{18}O enrichment. The latter data were obtained by quantitatively measuring the isotope-induced chemical shifts for the furan carbons adjacent to the oxygen.[10] To a stirred solution of **4*** (208 mg, 1.5 mmol) in 20 mL of $CHCl_3$ were added 10 μL of concentrated HCl and 1.2 equiv of PBA. The reaction was worked up as before to give 210 mg of the ^{18}O-enriched lactone **11**. By high-resolution ^{13}C NMR spectroscopy of the peak (ester carbon) at 80.1 ppm, two peaks were observed with the C–^{18}O peak being 0.024 ppm upfield from the C–^{16}O peak. High-resolution ^{13}C NMR spectroscopy of the lactone carbonyl at 174.8 ppm also showed two peaks, with the C–^{18}O peak shifted 0.011 ppm upfield of the C–^{16}O peak. Quantitative measurement of the peak showed 30% incorporation of isotope. GCMS analysis of the M + 2 peak showed 32% isotope incorporation. If any ^{18}O label had been in the lactone carbonyl oxygen, the expected change in chemical shift would be 0.04–0.05 ppm. *Thus because of the peaks found in the carbon spectrum at 80.1 ppm and the small chemical shift difference in the carbonyl carbon, we conclude that all the label was in the lactone ring oxygen.* On the basis of the NMR data and the GCMS data, we can also conclude that between 7 and 9% of the label was lost during the reaction.

Scheme I



Scheme II



(13) Tsuboi, S.; Shimozuma, K.; Takeda, A. *J. Org. Chem.* **1980**, *45*, 1517.