dropwise while stirring the reaction during 30 min. The mixture was stirred for an additional 12–16 h to ensure complete conversion. The reaction was stopped and the remaining dimethyl sulfate was neutralized with dilute ammonia. The organic phase was separated, washed, and evaporated, leaving the dimethyl ether as product.

Oxidation Procedure. The oxidations were performed in a 500-mL Parr hydrogenation apparatus (Model 3921). The reaction vessel was charged with substrate, solvent (benzene), catalyst, base, and internal GLC standard if necessary. The vessel was flushed five times with oxygen and then brought to a pressure of 75 psi. The reaction commenced by starting the shaker. After 2 h no further oxygen uptake was observable and the reaction was stopped. The reaction mixture was neutralized by 5% aqueous H_2SO_4 and then analyzed.

Analysis. In general, conversions were computed by GLC analysis. For reactions where the products were acids, dodecane was used as an internal standard. The column used was 15% OV-17 on acid-washed Chromosorb W with a Packard 427 gas chromatograph with FID detectors, column length 2 m, column temperature 100–200 °C at 10 °C/min. For all substrates the product was isolated at least once. For fluorenone and benzophenone, the water phase was separated and the benzene was evaporated. The remaining benzophenone and fluorenone were identified by IR and by their dinitrophenylhydrazine derivatives; benzophenone mp 236-237 °C, fluorenone mp 282-283 °C. For picolinic, nicotinic, and isonicotinic acids, water only was added to the reaction mixture and the benzene phase was separated. The water phase was then acidified with dilute HCl and the water was evaporated. From the remaining solid the carboxylic acid was dissolved in ethanol, which was then evaporated to leave the respective acid: picolinic acid, mp 135-136 °C; nicotinic acid, mp 233-234 °C; and isonicotinic acid, mp 314-315 °C.

Registry No. PEG, 25322-68-3; fluorene, 86-73-7; α-picoline, 109-06-8; β-picoline, 108-99-6; γ-picoline, 108-89-4; diphenylmethane, 101-81-5; triphenylmethane, 519-73-3.

Mechanism for the *m*-Chloroperbenzoic Acid Oxidation of Trialkyl-Substituted Furans

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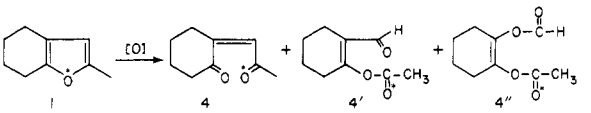
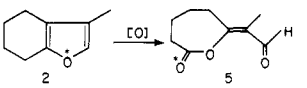
The impetus for investigating the oxidation of furan-containing compounds is derived from their potential toxicity.[1] They are known to be toxic to animals and man and in several cases have been shown to give enhanced activity when oxidized by the mixed function oxidase (MFO) enzyme system.[2]

We began our study on the oxidation of model furan compounds by investigating several reported chemical mimics of the MFO enzyme system. Of these, *m*-chloroperbenzoic acid (mCPBA) is the most readily available and easily controlled reagent[3] and was, therefore, our choice. There may be some question as to whether or not the peracid is, in fact, a reasonable mimic of the MFO. Nevertheless, the results gained in this study are intriguing and useful. In this paper, we present some new results that tie the previous papers together into a general reaction sequence for the peracid oxidations of these types of alkylated furan compounds.

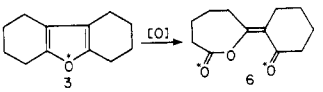
In previous work,[4,5] we have investigated the peracid oxidations of three compounds: 2-methyl- and 3-methyl-4,5,6,7-tetrahydrobenzofuran and perhydrodibenzofuran (eq 1–3). Further, through the use of ^{18}O label



(1)



(2)



(3)

(shown as an asterisk in eq 1), the pathway for the oxidation of compound 1 was elucidated and has been discussed in detail previously.[5] Briefly, compound 1 was shown to react with the first mole of mCPBA to form an epoxide at the *internal* and *more substituted olefin*. This epoxide then rearranges rapidly to the *enedione* 4 shown in eq 1 with the labeled oxygen going to the methyl ketone moiety. A second mole of mCPBA reacts at the methyl ketone moiety to form the acetate which rearranges to acetate 4′. Finally, a third mole of mCPBA reacts with the aldehyde functionality to form the formate ester shown as 4″. It is important to remember this sequence as reference is made to it later in the paper. For compounds 2 and 3, we had not executed any ^{18}O-labeling studies at the time of their publication and suggested in those two cases that an alternative diepoxide pathway might be a reasonable means to the observed products.

Results and Discussion

3-Methyltetrahydrobenzofuran (2). Compound 2 was readily labeled with ^{18}O by a method that has been published elsewhere.[6] It contained 43% ^{18}O label as determined by NMR spectroscopy. The ^{13}C NMR resonances for the atoms adjacent to ^{16}O were at 150.9 and 136.7 ppm, and the ^{13}C–^{18}O resonances occurred 0.039 and 0.036 ppm upfield, respectively.[7]

On oxidation with 2 equiv of mCPBA in CH_2Cl_2 at 0 °C, a nearly quantitative yield of lactone 5 was obtained (eq 2). NMR spectral analysis showed that >98% of the ^{18}O label was contained in the lactone carbonyl oxygen. The ^{13}C–^{16}O resonance for 5 was at 170.7 ppm with the ^{13}C–^{18}O resonance occurring 0.04 ppm upfield. This result is not definitive and is consistent not only with the diepoxide intermediate, which was proposed earlier,[4] but also with an enedione intermediate in analogy with the 2-methyl case.

Perhydrodibenzofuran (3). As in the previous example compound 3 was labeled with ^{18}O by a method published elsewhere.[6] It contained 39% ^{18}O as determined by NMR spectral analysis and 41% by mass spectral analysis. On oxidation with 2 equiv of mCPBA in CH_2Cl_2 at 0 °C,

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Table I. ^{13}C NMR Data on the ^{18}O-Labeled Furans and Products from Their Peracid Oxidation

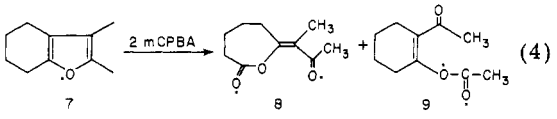
compd	chemical shift, ppm	$\Delta\delta$,[a] ppm	^{18}O, % NMR	^{18}O, % MS
2	150.9 (s)	0.039	43	44
	136.7 (d)	0.036	43	
3	148.4 (s)	0.039	39	41
5	170.7 (s)	0.040	41	42
6	201.5 (s)	0.050	20	39
	172.3 (s)	0.040	20	
7	147.8 (s)	0.040	44	45
	144.7 (s)	0.040	44	
8	200.2 (s)	0.049	15	40
	171.2 (s)	0.040	26	
9	168.5 (s)	0.010	26	41
		0.037	15	

[a] This is the ppm shift upfield for the ^{13}C resonance that is attached to the ^{18}O atom.

it was rapidly converted (~5 min) to the lactone ketone **6** in >96% yield. NMR spectral analysis of **6** revealed that the ^{18}O label was distributed equally between the lactone carbonyl (172.3 ppm) and the ketone carbonyl (201.5 ppm). This result is entirely consistent with an enedione intermediate, which makes the oxygens equivalent and thus rules out a diepoxide intermediate for this substrate. A diepoxide intermediate would always result in the labeled furan oxygen going solely to the lactone carbonyl.

2,3-Dimethyltetrahydrobenzofuran (7). Compound **7** was anticipated to react either as a unique substance or as a mixture of the 2- and 3-methyl-substituted furans. It was prepared readily from compound **2** by reaction with *n*-butyllithium followed by methyl iodide (75% isolated yield). Thus, ^{18}O-labeled **7** was readily available from the previously prepared **2**-^{18}O. The labeled compound contained 44% ^{18}O label as each of the NMR resonances at 147.8 and 144.8 ppm could be resolved into two lines with the ^{13}C–^{18}O resonance upfield by 0.04 ppm.

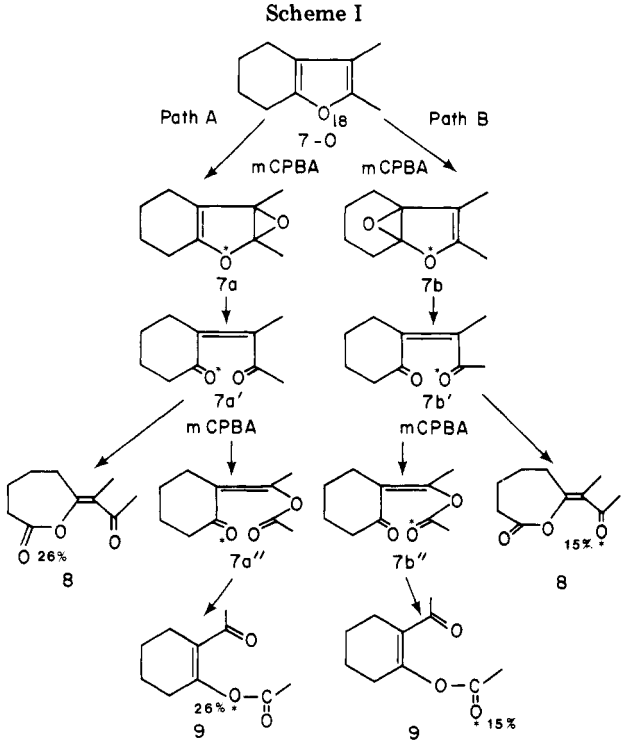
Oxidation of **7** under the usual conditions gave the results shown in eq 4, which indicated, by product type, that it was acting as a mixture of the 2- and 3-monomethyl analogues.



(4)

Compounds **8** and **9** were formed in nearly equal amounts with the ^{18}O labels as indicated by an asterisk. The carbonyl resonances for **8** were at 200.2 (ketone) and at 171.2 (lactone) ppm. The ester carbonyl carbon resonance for **9** was at 168.5 ppm. Thus in the ^{18}O-labeled products, the resonances for **8** were straightforward with a single upfield satellite resonance for the ^{13}C–^{18}O atoms (Table I). However, for **9**, the ester carbonyl resonance had two upfield peaks, indicating that two different ^{18}O atoms were attached to that carbon. Thus, from the ester ^{18}O atom, the ^{13}C was shifted upfield by 0.010 ppm, and from the carbonyl ^{18}O atom, the upfield shift was 0.037 ppm. Scheme I is presented to facilitate the discussion of how the ^{18}O distribution arises and thereby to show the pathways for product formation. The ^{18}O distribution in the reaction products occurred in two distinct pairs (see bottom of Scheme I). One pair contained 26% ^{18}O label and the other contained 15% ^{18}O. Thus, we concluded that **8** and **9** were formed in both. This then allows one to conclude that the ratio of **7a**:**7b**, which is 1.7, is a measure of the relative rates of epoxidation in the first step. Thus, it appears that compound **7** is epoxidized nearly twice as

Scheme I



fast at the olefin that is substituted by two methyl groups. Further, the fact that the product ratio **8**:**9** in each pair is nearly unity shows that the Baeyer–Villiger oxidation is without regioselectivity.

Conclusions

Since both compounds **8** and **9** are formed *equally* by *each* pathway as evidenced by the ^{18}O-labeling data and since **9** had previously been shown to result from an enedione intermediate, it is reasonable to suggest that they both come from the same enedione intermediate.

Further, since product **8** is analogous to product **5** (reaction 2), we, therefore, conclude that it too arises through an enedione intermediate. Thus in the mCPBA oxidations, it appears that all of these alkylated furan compounds proceed first by epoxidation, rearrangement to the enedione, and then by further oxidation by a second mole of peracid.

While there is similarity in mechanistic sequence, there are some intriguing differences between the pathways for the asymmetrically substituted compounds **1** and **2**. In the first step (epoxidation) compound **1** prefers to epoxidize at the internal and more substituted olefin while **2** prefers attack to occur at the least substituted external double bond. Second, although quantitative data were not collected, qualitatively compound **1** reacted considerably faster than **2** as it was difficult to keep the former at 0 °C during the reaction. Third, the Baeyer–Villiger oxidations of the enediones from **1** and **2** do not occur at the same site. Compound **1** reacts at the methyl ketone functionality rather than at the cyclohexyl ketone. Finally, these reactions are very fast ($t_{1/2} \approx 3$ min) compared to the normal Baeyer-Villiger reaction.

Experimental Section

General Methods. Proton and ^{13}C NMR spectra were collected on a Bruker WM250 spectrometer with $CDCl_3$ as solvent. Mass spectral data were obtained on a VG-16 spectrometer. Analytical samples were sent to Galbraith Laboratories, Inc. In the determination of ^{18}O incorporation by ^{13}C NMR spectroscopy, sweep widths of 500 Hz were typically used. Data was acquired in a 4K block and transformed as an 8K block followed by a 0.3-Hz

exponential multiplication factor. The $H_2{}^{18}O$ (99%) was obtained from Stohler.

Preparation of Furans 1-3 and Their ^{18}O Analogues. The synthesis for each of these compounds has already been reported in ref 4-6.

Oxidation of ^{18}O-Labeled 3-Methyl-4,5,6,7-tetrahydrobenzofuran (2-^{18}O). To a stirred solution of **2** (0.144 g, 1.1 mmol) in 20 mL of methylene chloride was added $NaHCO_3$ (0.2 g). The mixture was cooled to 0 °C and then mCPBA (0.456 g, 2.2 mmol, technical grade) was added in one portion. Stirring was continued 10 min at 0 °C. The reaction mixture was washed with 10% $Na_2S_2O_3$, 5% NaOH, and brine and dried over $MgSO_4$. Removal of solvent afforded 0.152 g of **5** (85%) as a clear oil. High-resolution ^{13}C NMR analysis of the resonances at 189.8, 164.8, and 123.9 ppm showed them all to be single lines in the proton-decoupled spectrum. However, the resonance at 170.7 ppm was resolved into two lines with the upfield resonance ($C^{18}O$) shifted by 0.040 ppm (41% ^{18}O). IR (neat) 1755 ($C^{16}O$), 1715 ($C^{18}O$) cm^{-1}. Mass spectral analysis showed 42% isotope incorporation.

Oxidation of ^{18}O-Labeled Perhydrodibenzofuran (3-^{18}O). To a stirred solution of mCPBA (0.76 g, 4.4 mmol) in 20 mL of methylene chloride at 0 °C was added a solution of **3** (0.38 g, 2.2 mmol) in methylene chloride (10 mL). After being stirred for an additional 10 min, the reaction mixture was washed with 10% $Na_2S_2O_3$, twice with 5% NaOH, and brine and dried over $MgSO_4$. Removal of solvent gave 0.37 g of **6** (82%) as a white solid. The resonance at 201.5 ppm was resolved into two lines with the upfield resonance shifted by 0.050 ppm. Comparison of the intensities of these lines showed 20% ^{18}O incorporation at this point. In a similar manner the resonance at 172.3 ppm was resolved with the upfield resonance shifted by 0.040 ppm. Analysis showed 20% ^{18}O incorporation at this site also. Mass spectral analysis showed 39% ^{18}O incorporation.

Preparation of 2,3-Dimethyl-4,5,6,7-tetrahydrobenzofuran (7). Following the procedure of Cohen,[8] a solution of *n*-butyllithium (7.3 mL, 12 mmol, 1.6 M in hexane, Aldrich) was added to a stirred solution of 3-methyl-4,5,6,7-tetrahydrobenzofuran (**2**) (1.58 g, 12 mmol) in 50 mL of tetrahydrofuran at -20 °C (ice-$CaCl_2$ slush) under a nitrogen atmosphere in one portion. To this yellow solution was added methyl iodide (1.80 g, 13 mmol, Baker). The reaction mixture was allowed to warm to room temperature and stirred for 4 h. At this point, 25 mL of water was added and the mixture extracted three times with pentane-ether (1:1). The combined extracts were washed with 5% $NaHSO_3$, three times with water, and brine and dried over K_2CO_3. Removal of solvent gave a yellow liquid which was chromatographed on silica gel. Elution with pentane afforded 1.67 g of a clear oil. Analysis by gas chromatography (SE-30 column) and ^1H NMR spectroscopy showed this material to contain 10% unreacted 3-methyl-4,5,6,7-tetrahydrobenzofuran (**2**) as well as the dimethylfuran **7**: ^1H NMR 2.59-2.47 (2 H, m), 2.37-2.25 (2 H, m), 2.17 (3 H, s), 1.83 (3 H, s), 1.86-1.65 (4 H, m) ppm; ^{13}C NMR 147.8 (s), 144.8 (s), 118.3 (s), 113.7 (s), 23.3 (t), 23.3 (t), 23.2 (t), 20.8 (t), 11.3 (q), 8.0 (q) ppm; IR (neat) 1605, 1450, 1390, 1370, 1270, 1255, 1230, 1165, 1150, 1100, 905 cm^{-1}; mass spectrum, *m/e* (relative intensity) 150 (M^+), 122 (100).

Oxidation of 2,3-Dimethyl-4,5,6,7-tetrahydrobenzofuran (7). To a stirred solution of **7** (0.78 g, 5.2 mmol) in 50 mL of methylene chloride at 0 °C was added dropwise a solution of mCPBA (1.78 g, 10.4 mmol) in methylene chloride (50 mL). This addition required 15 min and the reaction mixture was then stirred for 2 min. The mixture was washed with 10% $Na_2S_2O_3$ twice and with 5% NaOH and brine and dried over K_2CO_3. Removal of solvent yielded 0.87 g of a clear oil. Analysis by NMR spectroscopy showed this material to be 50% enol acetate **9** and 50% ϵ-lactone **8**. This material was chromatographed on silica gel. Elution with hexane afforded **9** as a clear oil: ^1H NMR 2.40-2.25 (4 H, m), 2.27 (3 H, s), 2.21 (3 H, s), 1.80-1.58 (4 H, m) ppm; ^{13}C NMR 198.4 (s), 168.5 (s), 155.0 (s), 126.1 (s), 30.5 (q), 28.8 (t), 25.0 (t), 22.3 (t), 21.8 (t), 21.3 (q) ppm; IR (neat) 1760, 1695, 1600, 1430, 1370, 1285, 1260, 1215, 1160, 1110, 1075, 920, 735 cm^{-1}; mass spectrum, *m/e* (relative intensity) 182 (M^+), 140, 125, 43 (100); TLC on silica gel, R_f 0.29 [hexane-ether (1:1)]. A sample for elemental analysis was prepared by preparative gas chromatography (SE-30 column). Anal. Calcd for $C_{10}H_{14}O_3$: C, 65.92; H, 7.74. Found: C, 65.74; H, 7.69. Elution with 10% ethyl acetate in hexane afforded **8** as a clear liquid: ^1H NMR 2.65-2.58 (2 H, m), 2.58-2.51 (2 H, m), 2.37 (3 H, s), 1.86 (3 H, s), 2.00-1.77 (4 H, m) ppm; ^{13}C NMR 200.2 (s), 171.2 (s), 154.5 (s), 124.5 (s), 33.7 (t), 31.8 (q), 31.1 (t), 26.0 (t), 23.3 (t), 13.3 (q) ppm; IR (neat) 1755, 1670, 1580, 1450, 1365, 1300, 1225, 1175, 1130, 1105, 1000, 915, 735 cm^{-1}; mass spectrum, *m/e* (relative intensity) 182 (M^+), 140, 99 (100), 43; TLC on silica gel, R_f 0.15 [hexane-ether (1:1)]. A sample for elemental analysis was prepared by chromatography on silica gel. Anal. Calcd for $C_{10}H_{14}O_3$: C, 65.92; H, 7.74. Found: C, 65.76; H, 7.78.

Oxidation of 7-^{18}O. To a stirred solution of **7**-^{18}O (0.39 g, 2.6 mmol) in 20 mL of methylene chloride at 0 °C was added dropwise a solution of mCPBA (1.20 g, 5.9 mmol, technical grade) in methylene chloride (30 mL). The addition was complete in 30 min. The reaction mixture was then washed with 10% $Na_2S_2O_3$, and twice with 5% NaOH and brine and dried over $MgSO_4$. Removal of solvent gave a clear oil, which was shown by NMR spectroscopic analysis to be 50% **8**-^{18}O and 50% **9**-^{18}O. This material was then chromatographed on silica gel. Elution with hexane afforded 0.14 g of **9**-^{18}O as a clear oil. The resonance at 168.5 ppm was resolved into three lines with one resonance shifted upfield of the main resonance by 0.010 ppm and the third resonance shifted upfield by 0.037 ppm. Comparison of the intensities of these lines showed 26% of the material to be associated with the resonance shifted by 0.010 ppm and 16% with the resonance shifted by 0.037 ppm: IR (neat) 1760 ($C^{16}O$), 1730 ($C^{18}O$) cm^{-1}.

Mass spectral analysis showed 41% incorporation of ^{18}O. Elution with 10% ethyl acetate in hexane afforded 0.13 g of **8**-^{18}O as a clear oil. The resonance at 200.2 ppm was resolved into two lines with the upfield resonance shifted by 0.049 ppm (15% ^{18}O). Similarly the resonance at 171.2 ppm was resolved into two lines with the upfield resonance shifted by 0.040 ppm (26% ^{18}O): IR (neat) 1755 ($C^{16}O$), 1730 ($C^{18}O$) cm^{-1}. Mass spectral analysis showed 40% incorporation of ^{18}O.

Registry No. **2**, 1919-00-2; **3**, 1010-77-1; **5**, 88888-86-2; **6**, 88888-87-3; **7**, 67722-28-5; **8**, 88888-88-4; **9**, 88888-89-5; *m*-chloroperoxybenzoic acid, 937-14-4.

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A Convenient and Simple Method for the α'-Chlorination of α,β and Conjugated Ketones

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A wide variety of synthetic reagents and methods are available for the synthesis of α-halo ketones, which are versatile synthetic intermediates.[1] These reagents and methods are however confined to the halogenation of saturated ketones or unsaturated ketones having the unsaturation remote from the carbonyl group. The specific α'-halogenation of α,β and higher unsaturated ketones has, by comparison, received very little attention.[2,3]

The α-halomethyl ketone function has found wide use in the design of site-specific reagents for affinity labeling of proteins.[4,5] To incorporate the α'-chloromethyl radical in α,β and higher unsaturated ketones as affinity probes for the visual pigment rhodopsin,[12] we have developed a

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