and 0.95 (ratios 1:4:4, respectively). Anal. Calcd for C_7H_9BrO: C, 44.47; H, 4.80. Found: C, 44.88; H, 5.09.

Bis(α-bromocyclohexyl) ketone (9) was prepared[1] in 58% yield, mp 100–101 °C (toluene–hexane). Electrochemical reduction at −0.18 V in HOAc/KOAc afforded α-acetoxydicyclohexyl ketone and dicyclohexyl ketone in a 3.5:1 ratio (VPC); reduction by mercury afforded the same two substances in a 10.4:1 ratio.

Acknowledgment. Financial support, including a postdoctoral fellowship for J.A., was provided by the National Science Foundation. Dr. L. Fitjer kindly supplied details on the synthesis of 4.

Registry No. 4, 60538-60-5; 5, 74605-55-3; 6, 1121-37-5; 7, 17346-16-6; 8, 3212-63-3; 9, 76447-11-5.

Oxidation of Benzyl Ethers[1]

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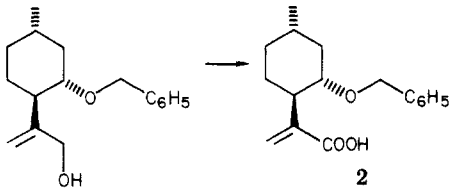
Received August 28, 1980

Benzyl ethers are commonly used to protect alcohols because of the ease of formation, stability to a variety of reagents, and specific removal methods.[2] In connection with a recent synthetic effort, the transformation of benzyl ether 1 into the corresponding acid 2 was required (eq 1).

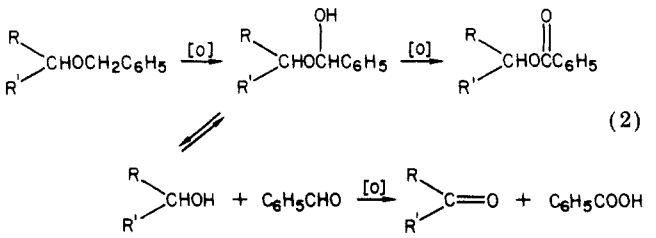


1 2 (1)

Jones reagent[3] seemed the logical choice to accomplish this goal; however, when compound 1 was allowed to react with Jones reagent at 0 °C for 1 h, a host of products resulted. These included the corresponding α,β-unsaturated aldehyde plus carboxylic acid(s) and a benzoate ester. Another reaction which was allowed to stir at 0 °C for 3–4 min gave only the aldehyde.

The oxidation of benzyl ethers with Jones reagent is a general one. Table I shows the results from the Jones oxidation of a variety of benzyl ethers.[4] For example, the benzyl ether of 2-octanol gives a 79% yield of 2-octanone and 21% 2-octyl benzoate in addition to 61% benzoic acid. In most of the systems studied, the ketone is formed in a larger proportion than the benzoate ester.

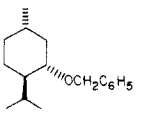
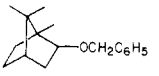
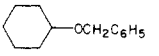
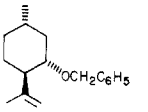
The products apparently arise by initial formation of a hemiacetal, as postulated in electrochemical oxidation of benzyl ethers,[5] followed by oxidation to the ester, ketone, and benzoic acid (eq 2). Exposure of 2-octyl benzoate to the reaction conditions and workup gave a 96% recovery of starting material, thus ruling out the benzoate ester as a precursor for the ketone and benzoic acid. In addition, the ratio of products does not change as a function of percent reaction.



(2)

The oxidation reaction is remarkably fast, using 4 equiv of Jones reagent[6] (see Table II). Thus, over half of the benzyl ether of 2-octanol is consumed within 20 min of combined addition and stirring time. In addition, the reaction is complete after 2.5 h. When only 1 equiv of

Table I. Jones Oxidation of Benzyl Ethers[a]

ether	products, % yield[b] ketone[c]	benzoate[c]	benzoic acid[d]
$CH_3(CH_2)_5CH(CH_3)OCH_2C_6H_5$	79	21	61
	57	28	53
$C_6H_5CH(CH_3)OCH_2C_6H_5$	56	21	52
	63	24	47
	16	40	16
	30	32	31

[a] All reactions were run for 12 h at 0 °C, using 4 equiv of Jones reagent. [b] (Millimoles/millimole of starting material) × 100%. [c] Average of percentages independently determined from GC and NMR data and weight of material obtained. [d] Isolated.

Table II. Rate of Oxidation of Benzyl Ethers[a]

addtn time, min	reacn time, min	% benzyl ether reacted[b]
2	5	55
10	10	57
10	30	61
10	60	67
10	100	80
10	110	87
10	155	100

[a] Using 2-octyl benzyl ether and 4 equiv of Jones reagent at 0 °C. [b] 100 × (millimoles of starting ether − millimoles of ether left)/millimoles of starting ether.

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(4) All benzyl ethers were prepared in over 90% yields from the corresponding alcohols with benzyl bromide and sodium hydride in dimethylformamide.

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(6) Although only 2–3 equiv of Jones reagent is required (see eq 2), the use of 4 equiv allows the reaction to go to completion without difficulty.

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Jones reagent is allowed to react with the benzyl ether of 2-octanol at 0 °C, using a 1-min addition and 4 min of stirring, 74% starting material is recovered in addition to 16% 2-octanone and 3% of the benzoate ester. Jones oxidation of 2-octanol is complete after a 1-min addition and 4 min of stirring under identical reaction conditions. Consequently, considerable benzyl ether oxidation will occur during alcohol oxidation with excess Jones reagent as these oxidations are often run.

Other chromium oxidizing agents were examined. For example, Collins reagent oxidizes alcohols to ketones in 15 min without affecting benzyl ethers;[7] however, after 15 h, 2-octyl benzyl ether gives 24% 2-octanone, 20% 2-octyl benzoate, and 45% starting material (the benzoic acid was not isolated). Pyridinium dichromate (PDC)[8] does not affect the benzyl ether of 2-octanol over a 16-h period.

There are several literature reports of oxidation of benzyl ethers.[9] For example, benzyl ether itself reacts with oxygen at elevated temperatures to give benzaldehyde, benzoic acid, benzyl benzoate, and toluene.[10] Benzaldehyde is produced from benzyl ethers and either uranium hexafluoride[11] or nitronium tetrafluoroborate[12] while electrolysis of benzyl ethers gives benzaldehyde and benzoate esters.[5] Benzyltriethylammonium permanganate converts benzyl ethers into benzoates[13] and chromium trioxide in glacial acetic acid yields esters from ethers.[14] In addition, there is one isolated report of the oxidation of a cyclic ether into a lactone with chromic acid in acetone.[15] Ruthenium tetroxide also effects the latter conversion[16] although benzyl ethers probably will be destroyed.[13]

In conclusion, oxidation of compounds containing benzyl ethers cannot be accomplished cleanly with Jones reagent if the desired oxidation is slow.[17] Collins reagent is an acceptable alternative for easily oxidized alcohols while PDC is satisfactory even for alcohols requiring prolonged reaction times.[18] Rapid oxidation by Jones reagent presents no difficulty.

Experimental Section

NMR spectra were recorded on a Varian T-60 spectrometer and IR spectra were obtained on a Perkin-Elmer 297 spectrometer. Melting points were run with a Thomas-Hoover melting-point apparatus. GC analyses were conducted with a Varian 90P instrument, using an SE-30 column.

Typical Oxidation Procedure. The benzyl ether (5.0 mmol) was dissolved in 100 mL of dry acetone and cooled in an ice bath. The Jones reagent[3] (4 equiv) was added dropwise over the appropriate period of time and the reaction was allowed to stir mechanically. The reaction mixture was quenched with ether and water and then extracted with four 50-mL portions of ether. The combined ether layers were washed with three 30-mL portions of saturated aqueous $NaHCO_3$, dried, and concentrated to give the benzoate ester, ketone, and benzyl ether if the reaction had not gone to completion. This mixture was analyzed by GC and NMR comparison with authentic samples. The combined $NaHCO_3$ extracts were acidified and cooled to 0 °C, and the benzoic acid was obtained by filtration. Melting point and NMR confirmed the identity of this product.

Registry No. Benzyl 1-methylheptyl ether, 67810-87-1; benzyl *p*-menth-3-yl ether, 76480-46-1; benzyl α-methylbenzyl ether, 2040-37-1; benzyl 2-bornyl ether, 76480-47-2; benzyl cyclohexyl ether, 16224-09-2; benzyl *p*-menth-8-en-3-yl ether, 76480-48-3; 2-octanone, 111-13-7; *p*-menthan-3-one, 89-80-5; acetophenone, 98-86-2; camphor, 76-22-2; cyclohexanone, 108-94-1; *p*-menth-8-en-3-one, 29606-79-9; 1-methylheptyl benzoate, 6938-51-8; menthol benzoate, 612-33-9; α-methylbenzyl benzoate, 13358-49-1; 2-bornanol benzoate, 20279-54-3; cyclohexyl benzoate, 2412-73-9; *p*-menth-8-en-3-ol benzoate, 76480-49-4; benzoic acid, 65-85-0.

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(17) At the very least, this is true when an α,β-unsaturated acid like compound **2** is desired.
(18) Allylic alcohols give only α,β-unsaturated aldehydes with PDC but saturated primary alcohols yield aldehydes or acids depending on the solvent.[8] Collins reagent gives only aldehydes from primary alcohols.[7]

Chemical Reduction of Actinomycin D and Phenoxazone Analogues to Free Radicals[1]

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Received September 3, 1980

The naturally occurring antibiotic actinomycin D (1, AMD) inhibits DNA-directed RNA synthesis[2,3] and is used clinically to treat Wilm's tumor, gestational choriocarcinoma, mixed metastatic embryonal carcinoma of the testes, and other tumors. In addition to the antibiotic's action of binding to DNA and inhibiting biochemical reactions involving DNA, the antibiotic causes chromosomal damage.[4,5] The clathrogenic nature of the antibiotic is not easily explained by simple DNA binding and appears to require active cell processes to occur. In our earlier investigations of AMD[6] we have shown that the phenoxazone ring system is capable of enzymatic single-electron reduction to a free radical intermediate with subsequent transfer of the electron to oxygen to yield superoxide. The similarity of quinone-containing antibiotics (for example, anthracyclines, mitomycin C, streptonigrin, etc.) and the quinonimine structure of AMD suggested the possibility of bioreductive capability of AMD that may fit the criteria of AMD being a "site-specific free radical".[7] We have proposed that some antibiotics are structurally prone to single-electron reduction to a free radical state and also have structural affinity for cellular components. As such "site-specific free radicals", these forms may be the critical activated form of the antibiotic to cause intracellular macromolecular damage and subsequent cell death.

In this work we have attempted to establish the chemical reductive nature of the quinonimine structure of AMD. We have utilized several chemical reducing agents and have followed the reaction by spectrophotometric and

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