Table I
pK_a Values of 2,6-Dialkylpyridinium Hydrochlorides in Several Solvents at 25°

Substituent	Methanol	50% Aqueous Ethanol	Water	Registry no.
H	5.37,[a] 5.4[b]	4.38[c]	5.22[e]	628-13-7
Me	6.86[a]	5.77[c]	6.72[e]	15439-85-7
Et	6.9[b]			54384-36-0
i-Pr	6.6[b]	5.34[c]		54384-37-1
t-Bu	4.2[b]	3.65,[d] 3.58[c]		54384-38-2

[a] Reference 6. [b] This work. [c] Reference 7. [d] Reference 8. [e] Reference 9.

Table II
Partial Molal Volumes of the Pyridinium Hydrochlorides at Infinite Dilution, and the Ionization Volumes in cm^3/mol in Methanol at 25.00°

Substituent	Φ_V°	ΔV_I°
H	63.69 ± 0.22	+9.8
Me	97.72 ± 0.19	+8.1
Et	128.39 ± 0.29	+10.0
i-Pr	164.36 ± 0.31	+10.8
t-Bu	196.02 ± 0.17	+22.0

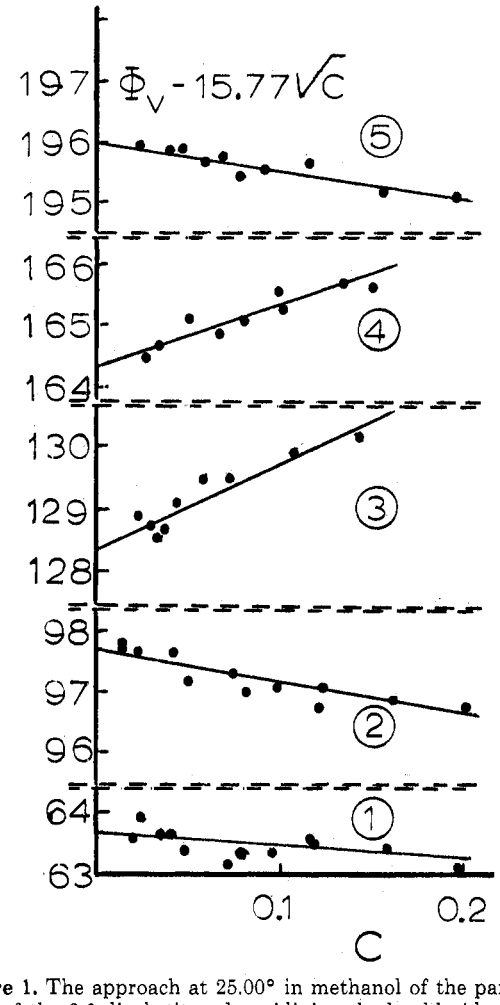

Figure 1. The approach at 25.00° in methanol of the partial volumes of the 2,6-disubstituted pyridinium hydrochlorides to their limiting values: (1) R = H; (2) R = Me; (3) R = Et; (4) R = *i*-Pr; (5) R = *t*-Bu.

pyridinium ions primarily on the grounds that the change at *tert*-butyl is so much more dramatic than with the other alkyl groups. He includes a stressed NH–SOH hydrogen bond as a possibility in his point of view. Our volume data do not allow a clear choice to be made between Brown's two possibilities; however, they do cast doubt on the hindered solvation. Solvation of ions is normally accompanied by a large volume decrease, and if this electrostriction were absent or greatly diminished in the *tert*-butyl cation, this should surely be reflected in an ionization volume much less than that of the lower homologs. What is observed is a volume change much *larger*, and even if allowance is made for the inability of the solvent to form hydrogen bonds with the neutral base, one would still have to conclude that there is no evidence for a conspicuous lack or absence of electrostriction around the cation.

Acknowledgment. This work was generously supported by the National Science Foundation.

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Blocking and Deblocking of α-Methylene-γ-butyrolactones[1]

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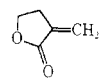
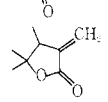
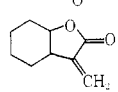
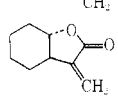
Recent reports in the literature have been concerned with the use of protecting groups which prevent Michael-type additions of nucleophilic reagents to the reactive sites of α-methylene lactones. These include dimethylamine,[3] thiols (1-propanethiol,[4] cysteine[5]), and phenylselenium anion.[6] We wish to report that sodium thiophenoxide can be employed in a high-yield reaction as a reagent for blocking α-methylene lactones. In addition, the removal of the β-phenylthio blocking group for regeneration of the α-methylene unit can be readily accomplished in high yield (see Table I) employing an alternate method from that previously utilized for β-thio adducts. Previously deblocking of a β-thio adduct required conversion to its corresponding

Table I

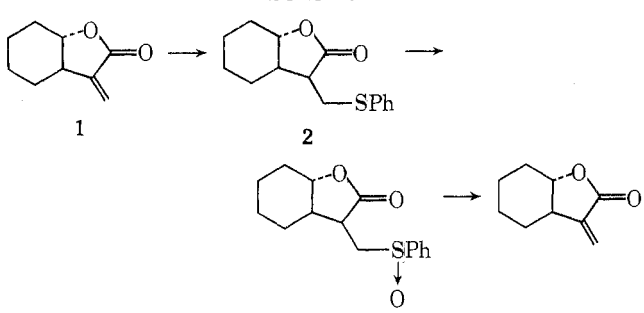
α-Methylene lactone	Registry no.	Yield[a] of β-thiophenyl adduct, %	Registry no.	Yield[a] of sulfoxide, %	Registry no.	Yield[a] of regenerated α-methylene lactone, %
	547-65-9	98	54353-61-6	95	54353-65-0	98
	49576-63-8	98.5	54353-62-7	99	54353-66-1	97
	16822-06-3	99	54353-63-8	99	54353-67-2	95
	3727-53-5	98	54353-64-9	97	54353-68-3	90

[a] Reported yields are based on isolated pure material.

sulfonium salt followed by β-elimination with aqueous sodium bicarbonate.[4]

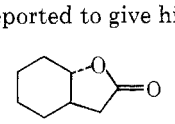
The blocking, deblocking sequence reported herein involves (a) addition of sodium thiophenoxide to the α-methylene lactone, (b) oxidation of the initially formed sulfide to its sulfoxide, and (c) thermal elimination of benzenesulfenic acid[7] (see Scheme I). Unlike our experience with

Scheme I



phenylselenium anion as a reagent for protecting the α-methylene function of lactones, the yields reported herein for the Michael addition are all nearly quantitative. Oxidation to the sulfoxide proceeds in greater than 95% yield with sodium metaperiodate at 0°. Heating the sulfoxide in toluene for 5 hr followed by evaporation of the solvent and distillation regenerates the α-methylene unit. Table I lists several other systems on which we have successfully carried out this sequence of reactions.

In principle, alkylation of a lactone enolate with iodomethyl phenyl sulfide should lead directly to a blocked α-methylene lactone. We have attempted to alkylate lactone **4** under conditions reported to give high yields of alkylated



products with alkyl iodides.[8] At best only a 20% yield of **2** could be realized employing **4** and iodomethyl phenyl sulfide. Attempts to improve this alkylation are in progress.

Experimental Section[9]

Addition of Sodium Thiophenoxide to α-Methylene Lactone 1. A solution of *trans*-butyrolactone **1** (106 mg, 0.7 mmol) in 2.0 ml of absolute ethanol was added at 0° to a solution of sodium thiophenoxide in absolute ethanol [prepared from sodium (25.8 mg, 1.12 mmol), ethanol (2.0 ml), and benzenethiol (308 mg, 2.8 mmol)]. The mixture was stirred at 0° for 1 hr. The reaction was quenched by the addition of acetic acid (4 drops) and water. Extraction with ether followed by washing of the combined ethereal extracts with water and brine afforded the crude β-thiophenyl adduct **2**. Purification by passage through a short column of silica gel resulted in 180 mg (98%) of pure material, mp 76.5–77°, which was homogeneous by TLC analysis (silica gel–methylene chloride). The NMR and ir spectra revealed lack of α-methylene protons [ir (CCl_4) 1775 and 1580 cm^{-1}].

Anal. Calcd for $C_{15}H_{18}O_2S$: C, 68.69; H, 6.92. Found: C, 68.83; H, 6.80.

Oxidation of Sulfide 2. A solution of sulfide **2** (131 mg, 0.5 mmol) in 7.0 ml of methanol containing 0.5 ml of benzene was treated at 0° with sodium metaperiodate (139 mg, 0.65 mmol) in 3.0 ml of water. After stirring for ca. 50 hr, the product was extracted with methylene chloride several times. The combined organic extracts were washed with water, dried ($MgSO_4$), and evaporated in vacuo, affording 188 mg of crude sulfoxide. Chromatography on silica gel [elution with benzene–ethyl acetate (1:1)] gave 135 mg (97%) of the β-phenylsulfinyl compound **3** which was homogeneous by TLC analysis (silica gel–methylene chloride) [ir (CCl_4) 3050, 1775, 1580, 1045 cm^{-1}].

Regeneration of α-Methylene Lactone 1 via Thermolysis. A solution of the β-phenylsulfinyl lactone **3** (135 mg, 0.48 mmol) in 5.0 ml of toluene was heated at ca. 107° for 5 hr. Evaporation of the solvent under reduced pressure afforded a crude oil (135 mg) which after distillation [75° (bath temperature), 0.2 mmHg] resulted in 66 mg (90%) of pure α-methylene-γ-butyrolactone **1**. The NMR and ir spectra were identical with those previously recorded[10] [ir (CCl_4) 1767 and 1668 cm^{-1}; NMR (CCl_4) δ 5.91 (C=CH_2, doublet, J = 3 Hz, 1 H), 5.34 (C=CH_2, doublet, J = 3 Hz, 1 H), 3.9–3.4 (broad, CHO–).

Acknowledgment. We thank the National Cancer Institute (Public Health Service Research Grant RO1 CA 13689-03) and Eli Lilly & Co. for generous support of our research. We thank Messrs. Steven Burke and Nebojsa Marinovic for preparing the starting α-methylene lactones.

Registry No.—Sodium thiophenoxide, 930-69-8.

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4-Oxahomoadamantane from Intramolecular, Nucleophilic Participation by Hydroxyl under Hofmann Elimination Conditions[1,2]

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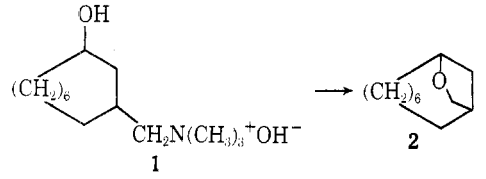
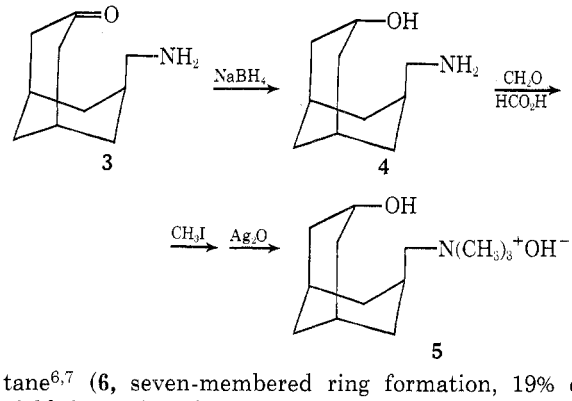
We are prompted by a recent report[3] to communicate our results on intramolecular, nucleophilic displacement under Hofmann elimination conditions. Hirsch and coworkers obtained[3] **2** (five-membered ring formation, 33% yield) by decomposition of the quaternary hydroxide **1** (eq 1) along with lesser quantities of other products.



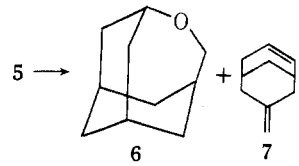
1 2 (1)

We investigated **5**, which was synthesized from *endo*-7-aminomethylbicyclo[3.3.1]nonan-3-one (**3**)[4,5] according to eq 2. Thermolysis of crude **5** produced 4-oxahomoadamantane[6,7] (**6**, seven-membered ring formation, 19% overall yield from **3**) and minor amounts of 7-methylenebicyclo[3.3.1]non-2-ene[5] (**7**, 2% overall yield from **3**) (eq 3).



3 4 5 (2)

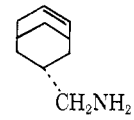
Since nucleophilic displacement of tertiary amines is known[8] to compete with straightforward elimination, this type of intramolecular alkylation process involving the alkoxide form of **5** appears reasonable.



6 7 (3)

A number of analogous examples are recorded in the prior literature.[8] The six-membered ether, thebenone, was generated from tetrahydrothebainonemethine by a similar process involving the phenolic hydroxyl. In addition, β-amino alcohol precursors gave rise to epoxides from participation by the neighboring hydroxyl group. Formation of *trans*-β-methylstyrene oxide from the quaternary hydroxide derived from ephedrine serves to illustrate. In the previous work,[3,8] cyclization involved formation of three-, five-, and six-membered rings.

Diolefin **7** most likely is formed by dehydration of **4** in the presence of formic acid, followed by exhaustive methylation and Hofmann elimination. Compound **4** is known to undergo partial dehydration to the corresponding amino alkene **8**[7] on exposure to 20% formic acid (1 day at reflux).[2,9]



8

Experimental Section

Compound **3** (9.3 g, 0.055 mol) was reduced in ethanol with sodium borohydride to the corresponding endo alcohol **4**.[10] After addition of water, the product was extracted with chloroform. Evaporation of the dried solution provided the desired material, which was subjected to the Hofmann elimination procedure.[5] The intermediates were not purified. A white, solid product, 4-oxahomoadamantane (**6**, 1.32 g, 17% overall yield from **3**) sublimed into the condenser during reaction. Identification was effected by comparison with spectral data for the authentic material.[6,11] The distillate from pyrolysis was extracted with ether. The organic layer was washed with dilute hydrochloric acid, then with water, dried, and freed of solvent. GLC analysis of the liquid product (0.3 g) revealed the presence of **6** (40%) and **7** (60%, 2% overall yield from **3**).

Acknowledgment. We thank Mr. T. A. Wnuk for helpful discussions.

Registry No.—**3**, 34650-78-7; **4**, 21933-00-6; **5**, 54517-88-3; **6**, 21898-86-2; **7**, 37439-70-6.

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