A Study of the Effects of Replacing Either of the Oxygens of the Ester Group by Sulfur and Selenium. Investigations of the Sulfur and Selenium Isologs of γ-Butyrolactone and of Phthalide[1]

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Abstract: To obtain information about the alterations of electron distribution brought about by replacing either of the oxygens of esters by sulfur or selenium, the dipole moments of a series of chalcogenic analogs of γ-butyrolactone and phthalide were measured. The relative basicities of the carbonyl oxygens of γ-butyrolactone, γ-thiolbutyrolactone, and γ-selenolbutyrolactone were examined by studying the interaction of these compounds with phenylacetylene. The results suggest that resonance forms in which a fractional negative charge is located on the heteroatom vicinal to the carbonyl group are of increasing importance in passing from esters to thiol esters to selenol esters.

It has been known for some time that replacement of either of the oxygens of esters with sulfur or selenium profoundly modifies the abilities of such compounds to undergo enzymic or nonenzymic reactions. Numerous comparative studies of the reactivities of analogous esters, thiol esters, and thiono esters have been carried out.[4]

Replacement of either of the oxygens of esters also modifies their hydrogen-bonding and hydrophobic-bonding capacities. These problems are of biological relevance since certain esters and thiol esters can play extremely important roles in cellular and biochemical processes. Thus, the thiol esters of coenzyme A are of pivotal importance in group or energy transfer reactions,[5] while the simple ester, acetylcholine, is the activator molecule, attachment of which to excitable membranes is claimed to induce the permeability changes required for transmission of the nervous impulse.[6]

Replacement of the sulfur of coenzyme A by selenium[7] or oxygen,[8,9] or replacement of either of the oxygens of acetylcholine by sulfur or by selenium, profoundly modifies the biological actions of these molecules.[10–12] Since the atomic radii and electronic characteristics of oxygen and of sulfur are rather different, it is not surprising that replacement of oxygen by sulfur may induce effects not limited to the ester group being modified, but may alter the conformation of the molecule as a whole. For instance, while the $-N^+CCO-$ grouping in acetylcholine is in the *gauche* conformation in the crystal[13] and in solution,[14] the $-N^+CCS-$ grouping in acetylthiolcholine is in the *trans* conformation in either environment.[15,16] Thus, when the enzymic and nonenzymic reactivities or the hydrogen-bonding and hydrophobic-bonding capacities of esters, thiol esters, and thiono esters are compared, it is difficult to tell whether the differences observed are due to steric or to electronic factors.

This problem can be approached by comparing isologous sulfur and selenium compounds which, because of the similarity of the atomic radii of sulfur and selenium, are essentially isosteric both in the crystal and in solution.[15–18] Since in spite of this steric similarity, the reactivities,[19,20] binding capacities, and biological actions[10–12] of the sulfur and selenium isologs of esters differ widely, the differences must be due to electronic rather than to steric factors. Because of these considerations, an investigation of the effects, on electron distribution, of replacing either of the oxygens of the ester group by sulfur and selenium was undertaken. Measurements of the dipole moments of lactones and their thio- and selenoisologs seemed to provide a good tool for studying the resonance interactions in esters, thiol

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(2) Public Health Service Fellow (2-F2-CA-15,695), 1962–1964.

(3) To whom requests for reprints should be addressed at: Department of Biochemistry and Pharmacology, Tufts University School of Medicine, Boston, Mass. 02111.

(4) For instance: L. H. Noda, S. A. Kuby, and H. A. Lardy, *J. Amer. Chem. Soc.*, **75**, 913 (1953); R. Schwyzer, *Helv. Chim. Acta*, **36**, 414 (1953); P. J. Hawkins and D. S. Tarbell, *J. Amer. Chem. Soc.*, **75**, 2982 (1953); R. Benesch and R. E. Benesch, *ibid.*, **78**, 1597 (1956); T. C. Bruice, *ibid.*, **81**, 544 (1959); W. P. Jencks, S. Cordes, and J. Carriuolo, *J. Biol. Chem.*, **235**, 3608 (1960); K. A. Connors and M. L. Bender, **26**, 2498 (1961); T. C. Bruice, J. J. Bruno, and W. S. Chou, *J. Amer. Chem. Soc.*, **85**, 1659 (1963); L. R. Fedor and T. C. Bruice, *ibid.*, **86**, 4117 (1964); T. C. Bruice and L. R. Fedor, *ibid.*, **86**, 4886 (1964); G. E. Lienhard and W. P. Jencks, *ibid.*, **87**, 3863 (1965); M. J. Gregory and T. C. Bruice, *ibid.*, **89**, 2121 (1967); S. C. Smith and R. J. Feldt, *J. Org. Chem.*, **33**, 1022 (1968).

(5) L. Jaenicke and F. Lynen, *Enzymes, B*, 3, 3 (1960).

(6) D. Nachmansohn, "The Chemical and Molecular Basis of Nerve Function," Academic Press, New York, N. Y., 1959.

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(11) H. G. Mautner, E. Bartels, and G. D. Webb, *ibid.*, **15**, 187 (1966).

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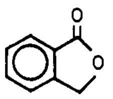
esters, selenol esters, and their thiocarbonyl and selenocarbonyl analogs.

In lactones the effect of the replacement of either of the oxygens of the -OC(=O)- grouping can be studied systematically, while the presence of this group in a rigid ring system minimizes differences in bond angles and molecular conformation induced by the replacement of the oxygen atoms by sulfur or selenium. We investigated the following phthalide and γ-butyrolactone isologs.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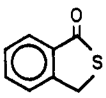
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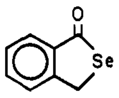
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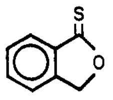
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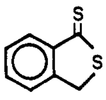
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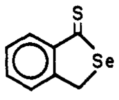
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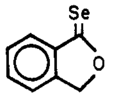
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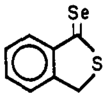
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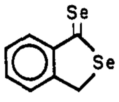
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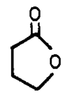
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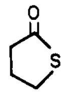
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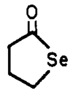
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Experimental Section

Materials. γ-Butyrolactone, γ-thiolbutyrolactone,[21] and γ-selenobutyrolactone[22] were purified by being vacuum distilled three times. A commercial sample of phthalide was recrystallized four times. Thiophthalide, selenophthalide, thionophthalide, thionothiolphthalide, thionoselenolphthalide, and selenocarbonylphthalide[23] were synthesized according to literature methods[24] and purified to constant ultraviolet extinction. Selenocarbonylthiophthalide was synthesized by the following procedure.

Selenocarbonylthiolphthalide. A solution of 7.4 g of iminothiolphthalide[24] in 80 ml of absolute methanol was added to a solution of 6.3 g of dry pyridine in 80 ml of chloroform with stirring. The mixture was kept under nitrogen and chilled in an ice bath. Hydrogen selenide was bubbled into the solution which rapidly became dark green. The reaction was permitted to proceed for 20 min; the solvent was then removed under suction at 40°. The residue was washed with ice-water and cold 1 *N* hydrochloric acid and then extracted with *n*-hexane. The organic layer was dried over magnesium sulfate. On chilling, dark green needles (1.5 g, 17.6%) separated from the solution. After three recrystallizations from *n*-hexane the product melted at 81-81.5°;[25] uv spectrum: ethanol, λ_{max} 304, 392 mμ; ϵ_{max} 12,730, 11,250.

Anal. Calcd for C_8H_6SSe: C, 45.00; H, 2.84; S, 15.11; Se, 37.05. Found: C, 45.15; H, 2.98; S, 15.34; Se, 36.87.

Dipole Moment Measurements. Spectrograde benzene, used as solvent for the dipole moment determinations, was dehydrated by passage through "Woelm" basic activity 1 alumina. The dielectric constant of the solvent was checked before every dipole moment determination. Cyclohexane was refluxed over sodium wire and fractionated before use. A WTW dipolmeter, Model DM-01 (Wissenschaftliche Technische Werkstätten GmbH., Weilheim, Germany), with a reading sensitivity of 7 × 10^{-6} was used for all measurements. A DFL-2 measuring cell, with a capacity of 4 ml and a thermostated jacket, to maintain the temperature of the solutions at 25.00 ± 0.03°, was employed.

For each dipole moment measurement, the dielectric constants were determined for the pure solvent and for a series of six solutions of increasing concentration. The weight fraction of solute in these varied from 0.0006 to 0.016. The density at 25.00° of the pure solvent and of each of the solutions was ascertained using a pycnometer with a capacity of 8 ml. Within the experimental error of the measurements, the dielectric constant–concentration and density–concentration plots were linear over the range measured, eliminating the possibility of significant intermolecular solute interaction.

Dipole moments were calculated by the dielectric constant and density extrapolation method of Halverstadt and Kumler.[26] The standard errors in the determination of the slopes of the (ϵ_{12} − ω_2) plots were obtained by the usual methods.[27,28]

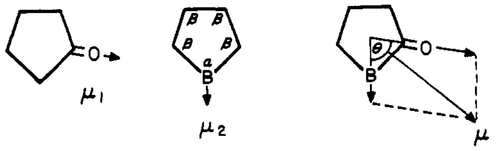
Electronic polarizations were derived from bond refraction values reported by Vogel[29] and Smyth.[30] A P_{E20} value of 13.1 was used for the C=Se group.[31]

Infrared Spectral Measurements. The measurements summarized in Table III were carried out with a Perkin-Elmer Model 21 spectrophotometer. The acetylenic C-H frequency of phenylacetylene was measured in 10-mm cells using 0.5% solutions of this compound in the presence and the absence of 2% wt/v of the lactones.

Results

The dipole moment data for the phthalide isologs and for the γ-butyrolactone isologs are summarized in Table I.

Dipole moments were found to decrease in passing from γ-butyrolactone to γ-thiolbutyrolactone to γ-selenolbutyrolactone. Calculation of the theoretical moments of the isologs was carried out using the assumption that the moments of the lactones should equal the resultants of the dipole moments of cyclopentanone (μ_1) and of tetrahydrofuran, tetrahydrothiophene, and tetrahydroselenophene (μ_2), respectively.



B = O, S, Se

The following relationship was used

$$\mu_{calcd} = \sqrt{(\mu_1^2 + \mu_2^2 + 2\mu_1\mu_2 \cos \theta)}$$

The bond angle was calculated using the equation

$$\theta = 180 - [(\alpha + \beta)/2]$$

where α is the bond angle around the heteroatom and β is calculated using the assumption that the remaining four bond angles of tetrahydrofuran, tetrahydrothiophene, and tetrahydroselenophene are equal. A value of 108° was used for the oxide, 92° for the sulfide, and 91° for the selenide angles, respectively.[32,33]

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[21] C. M. Stevens and D. S. Tarbell, *J. Org. Chem.*, **19**, 1996 (1954).

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[23] While the prefix thiono- refers to the thiocarbonyl group, the prefix selenono- refers to the $-SeO_2-$ grouping, according to *Chemical Abstracts* nomenclature; this leads to the rather awkward term selenocarbonyl ester.

[24] M. Renson and R. Collienne, *Bull. Soc. Chim. Belg.*, **73**, 491 (1964).

[25] Melting points were determined with a Gallenkamp melting point apparatus and corrected.

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[31] H. G. Mautner and W. D. Kumler, *J. Amer. Chem. Soc.*, **78**, 97 (1956).

[32] See ref 30, p 297.

[33] L. Pauling, "The Nature of the Chemical Bond," 3rd ed, Cornell University Press, Ithaca, N. Y., 1960, p 123.

Table I. Empirical Constants, Polarizations, and Dipole Moments (D)[a,b]

Compd	ϵ_1	ν_1	α	β	P	P_E	μ
I	2.2744	1.4411	18.44	−0.369	495.66	34.94	4.75 ± 0.01
II	2.2731	1.4414	13.75	−0.398	421.67	41.30	4.31 ± 0.01
III	2.2760	1.4394	9.50	−0.549	386.29	44.08	4.09 ± 0.02
IV	2.2745	1.4433	17.47	−0.388	526.90	42.16	4.87 ± 0.01
V	2.2747	1.4420	13.84	−0.389	469.74	48.49	4.54 ± 0.03
VI	2.2735	1.4431	9.57	−0.580	419.28	51.27	4.24 ± 0.04
VII	2.2735	1.4427	13.94	−0.542	551.75	44.75	4.98 ± 0.03
VIII	2.2732	1.4403	11.17	−0.553	485.04	51.08	4.61 ± 0.01
IX	Unstable						
X	2.2704	1.4412	21.97	−0.310	377.34	20.11	4.19 ± 0.01
XI	2.2702	1.4408	12.06	−0.446	320.41	26.38	3.83 ± 0.02
XII	2.2698	1.4412	9.58	−0.544	295.37	29.22	3.61 ± 0.02

[a] Measurements were carried out in benzene. [b] The symbols used are defined as follows: ϵ_1 dielectric constant, ν_1 specific volume, α slope of the $\epsilon_{12} - \omega_2$ plot, β_1 slope of the $\nu_{12} - \omega_2$ plot, P, molar polarization at infinite dilution, P_E, molar electronic polarization at infinite dilution, μ, dipole moment. Subscripts 1, 2, and 12 refer to solvent, solute, and solution, respectively.

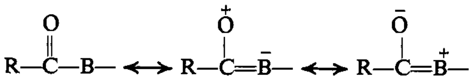
Table II. Calculated and Observed Dipole Moments of γ-Butyrolactone, γ-Thiolbutyrolactone, and γ-Selenolbutyrolactone (Benzene)

Compd	μ_1	μ_2	α, deg	β, deg	θ, deg	μ_{calcd}	μ_{found}
γ-Butyrolactone	2.93[a]	1.699[b]	108	108	72	3.80	4.19
γ-Thiolbutyrolactone	2.93	1.8[b]	92	112	78	3.80	3.83
γ-Selenolbutyrolactone	2.93	1.81[b]	91	112.5	78	3.75	3.62

[a] Reference 34a. [b] Reference 34b.

The results are summarized in Table II.[34a,b] It can be seen that the decrease in dipole moment observed in passing from γ-butyrolactone to γ-thiolbutyrolactone to γ-selenolbutyrolactone is greater (0.57 D) than the difference calculated (0.05 D).

There is ample evidence for resonance interaction between the carbonyl group and the adjacent heteroatom in esters, thiol esters, and selenol esters. In such compounds there is significant widening of the oxide,[35] sulfide,[36] and selenide[37] bond angles as evidenced by X-ray diffraction data. Similarly, there is significant shortening of the bond linking the heteroatom and the carbonyl group as compared to the expected heteroatom–carbon single bond value.[35–37] However, while the evidence for resonance is unequivocal, the question which resonance form predominates in esters, thiol esters, and selenol esters has been subject to some controversy.



$$R-\overset{\displaystyle O}{\overset{\|}{C}}-B- \longleftrightarrow R-\overset{\displaystyle \overset{+}{O}}{\overset{|}{C}}=\overset{-}{B}- \longleftrightarrow R-\overset{\displaystyle \overset{-}{O}}{\overset{|}{C}}=\overset{+}{B}-$$

B = O, S, Se

It has been postulated previously, on the basis of spectral evidence, that in thiol esters, utilization of d orbitals by the sulfur atom may play an important part.[38] The same conclusion was reached on the basis of the observation that thiol esters are considerably more acidic than isologous esters.[39] Similarly, involvement of 4 d orbitals has been invoked to account for the optical rotatory behavior of selenol esters.[40]

The dipole moment data summarized in Table II seem to indicate that in γ-selenolbutyrolactone resonance interaction results in the localization of a fractional negative charge on the heteroatom rather than on the carbonyl oxygen, while in γ-butyrolactone the opposite seems to be the case.

Since dipole moment measurements provide information only about electron distribution in the molecule as a whole, it seemed important to provide additional confirmation for this postulate. If it is valid, then there should be decrease in carbonyl basicity as the acyloxy oxygens of the lactones are replaced by sulfur and by selenium. It had been shown previously that the acetylenic C–H group of phenylacetylene was capable of interacting with electron donors and that these interactions lowered the C–H stretching frequencies by an amount dependent on the basicity of the donor atom.[41] This approach had been used by Baker and Harris[42] to show that the carbonyl oxygen in thiol esters has a lower ability to accept hydrogen bonds than the oxygens in analogous esters. Application of this method to the series γ-butyrolactone, γ-thiolbutyrolactone, γ-selenolbutyrolactone showed, as expected from the dipole moment measurements, a progressive decrease in the basicity of the carbonyl oxygen. These data are summarized in Table III.

Table III. Stretching Frequency of the C–H Group of Phenylacetylene in the Presence of γ-Butyrolactone, Its Sulfur and Selenium Isologs, and Related Compounds (in CCl_4)

Compd	$\nu_{C-H} \pm 3$
Control	3300
γ-Butyrolactone	3236
γ-Thiolbutyrolactone	3244
γ-Selenolbutyrolactone	3253
Cyclopentanone	3240
Tetrahydrofuran	3303

The dipole moments of the phthalide isologs are summarized in Table IV. It can be seen that the dipole

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(34) (a) A. L. McClellan, "Tables of Experimental Dipole Moments," W. H. Freeman and Co., San Francisco, Calif., 1963, p 142; (b) T. Strom, *et al.*, *J. Org. Chem.*, **33**, 2555 (1968).

(35) I. L. Karle and J. Karle, *Acta Crystallogr.*, **20**, 555 (1966).

(36) E. Shefter, *J. Pharm. Sci.*, **57**, 175 (1968).

(37) E. Shefter and O. Kennard, *Science*, **153**, 1389 (1966).

(38) G. Cilento, *Chem. Rev.*, **60**, 147 (1960).

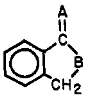
(39) G. E. Wilson, *Tetrahedron Lett.*, 2007 (1967).

(40) K. Bláha, I. Frič, and H. D. Jakubke, *Collect. Czech. Chem. Commun.*, **32**, 558 (1967).

(41) D. Cook, *J. Amer. Chem. Soc.*, **80**, 49 (1958).

(42) A. W. Baker and G. H. Harris, *ibid.*, **82**, 1923 (1960).

Table IV. Dipole Moments of Phthalide and of Its Sulfur and Selenium Isologs (Benzene, D)

		A =		
	B =	O	S	Se
	O	4.75	4.86	4.98
	S	4.31	4.53	4.61
	Se	4.09	4.24	Unstable

moments of phthalide, thiolphthalide, and selenolphthalide are higher than those of the corresponding γ-butyrolactone analogs. Obviously, there is resonance interaction with the benzene ring, this interaction being similar for all the benzbutyrolactone analogs. The decreases in dipole moment induced by the replacement of the noncarbonyl oxygen by sulfur and selenium are similar to the decreases induced by analogous substitution in the γ-butyrolactone series.

When the carbonyl oxygen of phthalide (or its thiol ester and selenol ester analogs) is replaced with sulfur and selenium a slight but meaningful increase in dipole moment is observed. However, this increase is much smaller than that noted when the carbonyl oxygen of amides is replaced by sulfur and by selenium.[31,43] The relatively high dipole moments of thioamides and selenamides, relative to those of their oxygen isologs, had been attributed to the progressively increasing contribution of charge-separated forms of the type $-NH^+=C(-B)$ as the carbonyl oxygen was replaced with sulfur and selenium, atoms in which octet expansion is possible. This postulate could be confirmed, when it was found that in isologous amides, thioamides, and selenamides the bond orders of the C=O, C=S, and C=Se bonds decreased in the order stated, while the bond orders of the vicinal C-N bonds increased.[17] Furthermore, acidity increases in passing from carbamyl to thiocarbamyl to selenocarbamyl compounds. Such interactions are, of course, less likely in esters than in amides and, thus, the relatively small increases in the dipole moments of the phthalide isologs induced by replacing their carbonyl oxygens with sulfur and selenium are not surprising.

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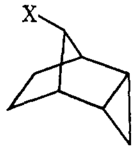
(43) M. H. Krackov, C. M. Lee, and H. G. Mautner, *ibid.*, **87**, 892 (1965).

Communications to the Editor

Edge Participation by Cyclobutane in a Bridged Homocyclobutylcarbinyl System

Sir:

Extensive edge participation at a developing carbonium ion center by a cyclopropane ring structurally if not spatially removed from the reaction site has been amply demonstrated in the 7-norbornyl systems **1**[1] and **2**.[2] Although the literature records no relevant



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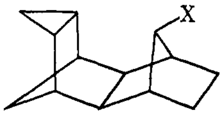

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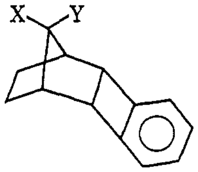
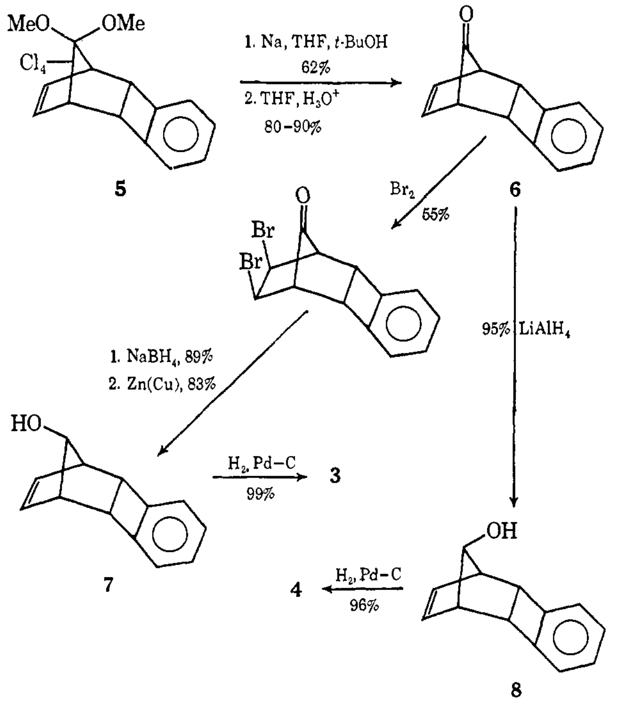


3, X = OH; Y = H
4, X = H; Y = OH

examples of cyclobutyl participation, similar, though less extensive, "edge" participation can be envisaged for the four-membered ring on the basis of theoretical estimates[3] of the deviation from rectilinear bonding in the smaller cycloalkanes. Again, incorporation of the cyclobutane ring into a rigid 7-norbornyl skeleton should provide the most favorable geometry for participation. In this communication we describe the synthesis and solvolytic reactivity of two such bridged derivatives, *endo-anti*-benztricyclo[4.2.1.0^{2,5}]non-3-en-9-yl brosylate (**3**-OBs) and its *endo-syn* isomer **4**-OBs, which provide direct insight into the question of cyclobutyl participation.

The epimeric alcohols essential to this study were prepared according to the scheme outlined in Chart I.

Chart I



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(2) M. A. Battiste, J. Haywood-Farmer, H. Malkus, P. Seidl, and S. Winstein, *ibid.*, **92**, 2144 (1970).

(3) C. A. Coulson and T. H. Goodwin, *J. Chem. Soc.*, 2851 (1962); 3161 (1963).