cis isomer the same proton appears as a doublet at δ 4.30. The peak for the single proton on the C-2 carbon atom is centered at *ca.* δ 3.94 in compound 8, while in compound 9 this same proton appears at δ 3.38 and is part of the three-proton multiplet that includes the two protons on C-3. This additional shielding of the C-1 and C-2 protons in 9 is probably due to the *cis* configuration of these protons. It appears that the chemical shift of the protons on the C-3 position is not effected by the stereochemistry at C-1 and C-2.

The olefinic compound, the slowest moving component, had a retention time on vpc identical with that of 1,2-diphenylindene (4). Compound 4 as indicated before, isomerizes to the 2,3 isomer under these vpc conditions and therefore could not be isolated by preparative vpc. In addition, compounds 8 and 9 could not be separated from compound 4 by column chromatography on Florisil. The structure of this compound had to be established by an alternative method as follows: an authentic sample of 1,2-diphenylindene (4) was isomerized to the 2,3 isomer (5) by a known procedure[12] in the presence of hot alcoholic potassium hydroxide. The melting point (108°) of the pale yellow crystals obtained on recrystallization from ethanol corresponds with that reported for this compound (5).

Thin layer chromatography on silica gel with 99:1 petroleum ether–benzene as the eluent gave an excellent separation of the two isomeric diphenylindenes; the 2,3 isomer (5) moved much faster than the 1,2 isomer (4). We were thus able to establish that in the above reaction mixture the olefin formed was indeed 1,2-diphenylindene (4).

Catalytic Hydrogenation of 1,2-Diphenylindene (4).—A solution of 200 mg of 4 in 50 ml of ethanol was hydrogenated in the presence of 250 mg (0.93 mmol) of 5% palladium on charcoal at 50 psi. After 30 min the catalyst was removed, and the filtrate was concentrated to 15 ml and allowed to crystallize. The fine white needles were collected to yield 150 mg (0.56 mmol, 60%) of *trans*-1,2-diphenylindan (8), mp 119–121°. Sublimation at 100–110° (0.1 mm) raised the melting point to 125–126° (lit.[12] mp 126°).

Catalytic Hydrogenation of 2,3-Diphenylindene (5).—To 100 mg of 10% palladium on charcoal there was added a solution of 1

g of 5 in 150 ml of benzene. This mixture was hydrogenated under 30 psi for 5 hr. After filtration through Celite and evaporation of the solvent, there was found by vpc analysis *cis*-1,2-diphenylindene (9) and unchanged 5 in the ratio of 1:2.2. Compound 9 and 5 were separated by preparative vpc and their identities were confirmed by their ir spectrum.

Reduction of 2-Phenyl-1-indanone and 2-Phenyl-1,3-indandione (10,1).—Separation of 2-phenylindan (11) and 2-phenylindene (12) was achieved by column chromatography. From the petroleum ether fraction, 11 was obtained as a colorless oil, which was distilled *in vacuo* at 100–110° (0.1 mm). The reported[15] boiling point for this compound is 165° (11 mm).

The second component, 2-phenylindene (12), was present in the 9:1 petroleum ether–benzene eluate. Shiny white flakes were collected on evaporation of the solvent. On recrystallization from hexane these melted at 167–168° (lit.[16] mp 167.5°). Correct analysis was obtained for a $C_{15}H_{12}$ hydrocarbon, and the ultraviolet spectrum (high ε) confirms that this is a conjugated unsaturated compound. The nmr spectra of 11 and 12 are included in Table II.

Reduction of the Dimer of 2-Phenyl-1,3-indandione (13).—Separation of 2-phenylindan (11) and 2-phenylindene (12) from the reaction mixture was achieved by column chromatography as in the previous reduction. Identity of these compounds with 11 and 12 obtained from the reduction of 1 was established by boiling points, mixture melting points, and infrared spectra. Isolation, characterization, and proposed structure of 14 are described in detail earlier in the paper.

Circular Dichroism of Monocyclic and Bicyclic Lactones. Restricted and Rigid Model Compounds for the Ester Chromophore

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The optical properties of monocyclic dilactones and of bicyclic bridged lactones have been examined using circular dichroism. In the 210–220-mμ region, the sign of the Cotton effect for the monocyclic dilactones (*S,S*)-3,6-dimethyl-1,4-dioxane-2,5-dione (I) and (*R,R*)-3,6-diphenyl-1,4-dioxane-2,5-dione (II) is opposite that of acyclic model compounds. Two new dichroic bands at 210 and 199 mμ have been observed in the circular dichroism spectra of 1,8,8-trimethyl-3-oxabicyclo[3.2.1]octan-2-one (III). Solvent and conformational effects on the dichroic properties of this bridged lactone (III) are assignable, because the molecule is essentially conformationally rigid.

Ultraviolet (uv),[1] optical rotatory dispersion (ORD),[2] and circular dichroism (CD)[3] studies of saturated lactones have recently attracted considerable attention.

The relationship between conformation and absolute configuration of these compounds and sign and magnitude of long-wavelength Cotton effects has been studied extensively. Four different approaches to this problem have been made independently by Klyne,[4] Snatzke,[5] Wolf,[6] and Legrand.[7]

The growing interest in the stereochemistry of optically active polyesters[8] prompted us to examine the rotatory properties of mono- and bicyclic lactones, since we believed that the transitions involved in the

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polymers could be more clearly assigned by studying low molecular weight, optically active materials.

In this context we wish to report our CD results on three lactones: (S,S)-3,6-dimethyl-1,4-dioxane-2,5-dione (dimethylglycolide or lactide) (I); (R,R)-3,6-diphenyl-1,4-dioxane-2,5-dione (diphenylglycolide or mandelide) (II); and 1,8,8-trimethyl-3-oxabicyclo-[3.2.1]octan-2-one (campholide) (III).
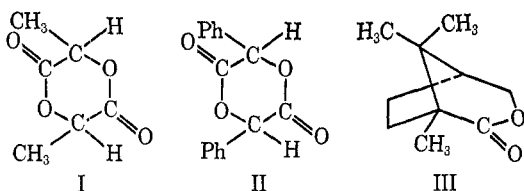
Compound III has a rigid conformation, while I and II have flexibility. In none of these cyclic esters, however, can the carboxylate group rotate about its C–C$_\alpha$ bond, as it can in open-chain esters.

In 1967, Closson[1a] investigated the isotropic absorption spectra of medium-sized unstrained *cis* lactones, whose carboxylate ester functions are planar because of resonance between the ether oxygen and carbonyl group. The solvent sensitivity of the n → π* transition of the ester chromophore was found to be greater for *cis* than for *trans* conformations (as in open-chain and large-ring esters). Medium-sized lactones show long-wavelength absorption maxima at 218–220 mμ in nonpolar solvents and at 209–213 mμ in polar solvents.

Few papers on the CD of saturated lactones have appeared,[3a-8] compared with the large number on ORD measurements. Wolf[3a] first reported CD data on steroid δ-lactones. The long-wavelength Cotton effect was found at about 235 mμ in isooctane. Seven γ-lactones of aldonic and related acids and two δ-lactones have been examined by Beecham.[3b] In water, the n → π* maxima appear at 219–220 mμ.

Circular dichroism has been used to elucidate the stereochemistry of gibberellins, which contain a γ-lactone chromophore in a gibbane skeleton. A band at about 225 mμ in ethanol has been reported.[3c]

In an excellent review on optical rotation,[3d] Urry demonstrated the presence of a 218-mμ CD band for (S)-homoserine-γ-lactone in water. The position of the band, its red shift on decreasing solvent dielectric constant, and its large anisotropy allow assignment of this Cotton effect to the n → π* transition of the ester chromophore. Unexpectedly, the detailed theoretical and experimental information of the peptide n → π* transition does not appear to be directly transferable to the transitions of the ester chromophore, since an α-amino group at exactly the same spatial position in the lactam imparts a negative rotatory power to the cyclic amide 210-mμ transition, and in the lactone a positive rotatory power to the cyclic ester 215-mμ transition.

Results and Discussion

As part of our study on the effect of conformational restriction and rigidity of molecules,[9] we have examined the CD spectra of mono- and bicyclic lactones I, II, and III. A comparison with acyclic analogs has also been made.
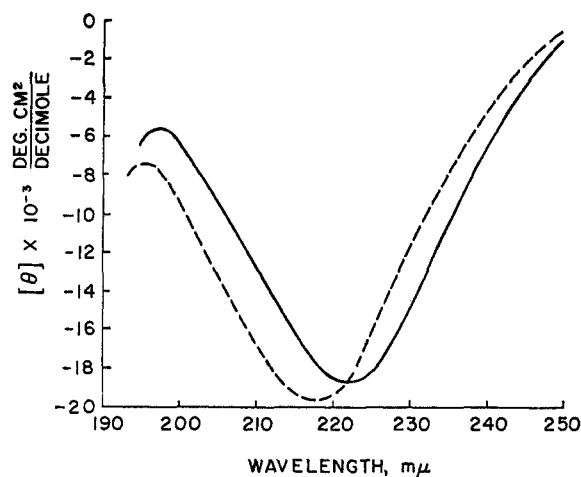

Figure 1.—CD spectra of (S,S)-3,6-dimethyl-1,4-dioxane-2,5-dione (I) in trimethyl phosphate (———) and in hexafluoro-2-propanol (-----).

A. (S,S)-3,6-Dimethyl-1,4-dioxane-2,5-dione [(S,S)-Lactide] (I).

—The isotropic absorption spectrum of (S,S)-lactide (I) shows a maximum at 207 mμ (ε 228.8) in methanol.[8a] Only the beginning of a large negative Cotton effect was detected in the ORD spectrum of this compound.[8a] Since both (S)-lactic acid[10,11a] and methyl O-acetyl-(S)-lactate[8b] exhibit a positive Cotton effect, centered in the 210–220-mμ region, arising from the n → π* transition of the carboxylate chromophore, we were interested in determining the sign of the 220-mμ band of (S,S)-lactide by CD to avoid the equivocation possible in ORD spectra. The background rotation of the negative Cotton effect could be sufficiently large to obscure a small positive Cotton effect set upon it.

The CD spectra of (S,S)-lactide (I) in hexafluoro-2-propanol and in trimethyl phosphate are shown in Figure 1.

The assignment of the long-wavelength negative band as an n → π* band is tenuous.[11b] A second negative band appears below 190 mμ. This band is probably related to the π → π* transition of the chromophore.

The inversion in sign of the n → π* ester band when methyl O-acetyl-(S)-lactate cyclizes to (S,S)-lactide does not appear in the amide series when N-acetyl-(S)-alanineamide[12] cyclizes to (S,S)-alaninediketopiperazine.[3d] Hence, our results on six-membered-ring dilactones, relative to diketopiperazines, agree with Urry's findings[3d] on the different behavior of five-membered-ring cyclic esters and amides.

In addition, we confirm[8b] that the dissimilarities in the circular dichroism between poly-(S)-lactic acid and (S,S)-lactide may depend on the cyclic nature of the lactide. As a result, acyclic diesters are better models for polyesters than dilactones. In the peptide system, however, cyclic amides, such as diketopiperazines, are considered prototypes of polypeptide structures insofar as their optical properties are concerned.[13]

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(12) J. A. Schellman and E. B. Nielsen in "Conformation of Biopolymers," Vol. 1, G. N. Ramachandran, Ed., Academic Press, Inc., New York, N. Y., 1967, p 109.

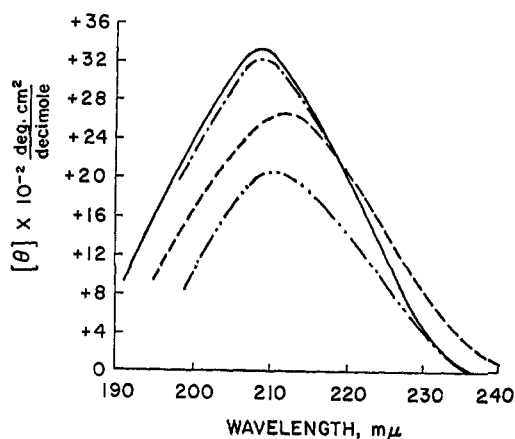(13) D. Balasubramanian and D. B. Wetlaufer in ref. 12, p 147.

Figure 2.—CD spectra of (S)-lactic acid in trifluoroethanol (———), in trimethyl phosphate (———), and in aqueous solutions at pH 2 (—·—) and 9 (—··—).
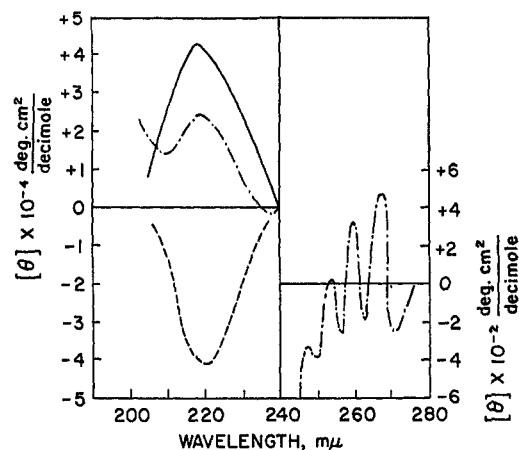

Figure 3.—CD spectra of (R,R)-3,6-diphenyl-1,4-dioxane-2,5-dione (II) in hexafluoro-2-propanol (—·—), (R)-mandelic acid in trifluoroethanol (———), and (S)-mandelic acid in trifluoroethanol (———) in the 205–245-mμ region, and of II in the 245–275-mμ region.

To obtain further information on the transitions involved in the carboxyl chromophore, we examined the far-uv (190–235 mμ) CD spectra of (S)-(+)-lactic acid[11] in solvents of different polarity and at different pH's. The positive CD band red shifts on changing solvent from trifluoroethanol (208 mμ) to trimethylphosphate (212.5 mμ) (Figure 2), indicating that this absorption arises from the n → π^* transition of the chromophore. The ionization of the carboxyl group appears to decrease the ellipticity of the n → π^* transition of the α-hydroxy acid, probably because of the greater symmetry of the ion. The maximum of the positive Cotton effect shifts slightly in going from pH 2 (208 mμ) to pH 9 (210 mμ). In contrast, Legrand and Viennet[14] reported a 7-mμ blue shift from the un-ionized form (217 mμ) to the ionized form (210 mμ) of a steroid hydroxy acid in ethanol. These results indicate that the location of the n → π^* band of the carboxyl chromophore is sensitive to solvent only when the group is un-ionized.

B. (R,R) - 3,6 - Diphenyl - 1,4 - dioxane - 2,5 - dione [(R,R)-Diphenylglycolide (II).—We also examined (R,R)-diphenylglycolide (II) using circular dichroism and compared results with those of (R)-mandelic acid and methyl (R)-mandelate. These compounds contain aromatic and carboxylate chromophores whose optical properties have recently been extensively reviewed.[15,16]

A monoalkylated benzene chromophore exhibits two transitions in the 270–190-mμ region: a very weak band at about 260 mμ, which shows fine structure, classified $'L_b$ in the Platt notation;[17] and a stronger band ($'L_a$) at about 210 mμ, also forbidden but probably involving a contribution from the first allowed π → π^* transition which overlaps it at shorter wavelengths.[18]

The optical activity of these aromatic transitions has been shown independently by Moscowitz[19] and Verbit.[20–22] They report two CD bands centered at 260 and 222 mμ. The carboxyl and related chromo-

phores (such as ester and lactone chromophores) are also optically active. Their CD spectra show a solvent-dependent Cotton effect in the 210–220-mμ region.[3a–d,11,14,22–24]

The CD spectra of (R,R)-diphenylglycolide (II) in hexafluoro-2-propanol and of (R)- and (S)-mandelic acids in trifluoroethanol are shown in Figure 3.

(R)-Mandelic acid shows a series of well-resolved positive Cotton effects in the near-ultraviolet region, at about 258 mμ. We assign this band with vibrational fine structure to the $'L_b$ transition of the monosubstituted benzene chromophore. In the far-ultraviolet region, the hydroxy acid exhibits a negative CD band, centered at 220 mμ, which probably involves the contribution of both the $'L_a$ transition of aromatic compounds and the n → π^* transition of carboxylic acids. It is well established that two overlapping Cotton effects produce a spectrum from each of the component bands.[25]

The CD pattern of methyl (R)-mandelate in trifluoroethanol is very similar to that of the un-ionized parent acid (Table I). The replacement of the carboxyl

TABLE I

Location in Millimicrons and Molar Ellipticity Values (θ) of Dichroic Bands of Methyl (R)-Mandelate

Solvent	
Trifluoroethanol	267 (+390), 261 (+490), 254 (+320), 249 (+100), 219 (−44,000)
Isooctane	268 (+240), 262 (+260), 257 (+260), 250 (+50), 222 (−53,700)

with the carboxylate chromophore does not appear to involve any significant change in the dichroic properties of the α-hydroxy acid. In isooctane the Cotton effects of the ester are red shifted by 1–3 mμ (Table I). The ellipticity values decrease for the 260-mμ band and increase for the 220-mμ band. Upon ionization of the carboxyl group (pH 9), a general decrease in ellipticity for all the Cotton effects is observed.

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(25) K. M. Wellman, P. H. A. Laur, W. S. Briggs, A. Moscowitz, and C. Djerassi, *J. Amer. Chem. Soc.*, **87**, 66 (1965).

Since the signs of the Cotton effects at about 260 mμ are the same for (R)-mandelic acid, (R)-phenylglycine,[26] (S)-α-phenylbutyric acid,[27] (S)-α-phenylethylamine,[28,29] and (S)-α-phenylethyl alcohol,[29] Brewster's concept of rotationally important interactions of an α-carboxyl group and of α heteroatoms (such as oxygen or nitrogen) with a phenyl chromophore are supported.

The CD spectrum of (R,R)-diphenylglycolide (II) in hexafluoro-2-propanol exhibits several small but well-resolved Cotton effects in the 245–275-mμ region. In the far-ultraviolet region, two more bands at 240 and 219 mμ are observed. The limited solubility of compound II hampers systematic solvent-effect studies. If we compare the CD curve of compound II in hexafluoro-2-propanol with that of methyl (R)-mandelate in trifluoroethanol, significant differences in the number of Cotton effects and in their location and sign are apparent.

The completely different vibronic structures of ^1L_b aromatic transitions, the presence in the dilactone spectrum of a small negative band at 240 mμ which is not visible in the spectrum of the open-chain ester, and the opposite signs of the 219-mμ bands suggest complicated interactions between the two lactone and the two phenyl chromophores.

It is well established that, in conformationally mobile systems, the observed CD curve is composed of the population-weighted contributions of the Cotton effects of all species present.[30–32]

The dissimilarity in dichroic properties of methyl (R)-mandelate and (R,R)-diphenylglycolide confirm that great caution must be exercised in choosing models for optically active polyesters.

C. 1,8,8-Trimethyl-3-oxabicyclo[3.2.1]octan-2-one (Campholide) (III).—To distinguish between solvent and conformation effects on the optical properties of compounds containing the cyclic ester chromophore, we synthesized and studied the circular dichroism of the bridged ring lactone III, whose rigid bicyclo[3.2.1.]-octane skeleton does not allow conformational flexibility. It has been noted[33] that the first ORD extremum of the ester Cotton effect in bridged lactones occurs at slightly higher wavelengths (233–235 mμ) than in simpler unbridged lactones (225–227 mμ). This corresponds to a uv solvent-dependent shoulder at 215–218 mμ.[33,34]

We carried out CD studies on compound III in a number of solvents of different polarity (Figure 4).

The long-wavelength Cotton effects exhibit ellipticity values lower than those expected from the rigid molecular structure of the bicyclic material.

Surprisingly, in the 195–250-mμ region, two positive bands appear at about 225 and 199 mμ in hexane, acetonitrile, methanol, and trimethyl phosphate. In water, trifluoroethanol, and hexafluoroacetone tri-
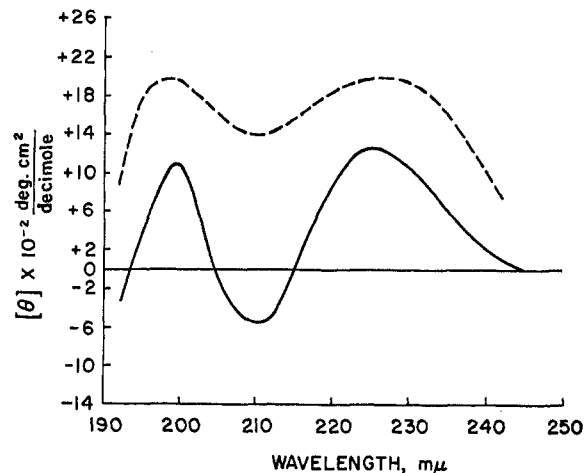

Figure 4.—CD spectra of 1,8,8-trimethyl-3-oxabicyclo[3.2.1]-octan-2-one (III) in hexane (– – –) and in trifluoroethanol (——).

hydrate, three bands appear—a negative band at 207–213 mμ and two positive bands at about 225 and 199 mμ. The three polar solvents thus reveal a negative Cotton effect, intermediate in location between the two positive dichroic bands and possibly masked in the curves in the less polar solvents.

Previous ORD[2a–d] and CD[3a–d] studies on lactones have not shown more than one complete Cotton effect, usually centered in the 215–220-mμ region and assigned to the n → π* transition of the chromophore. The beginning of a second dichroic band, centered below 200 mμ, has also been reported.[3d]

Since three bands appear for the rigid lactone III in polar solvents, where a transition-splitting phenomenon caused by dimeric association of the molecule or where conformational effects related to structural flexibility do not appear to be possible, the chromophore itself must undergo three transitions. This is analogous to the possible contribution of an n → σ* transition (between the n → π* and π → π* transitions) to the CD spectra of compounds containing the amide chromophore, as indicated by three very recent studies.[3d,35,36]

Thus the solvent effect on the energy levels of the chromophore appear to play an important role in bringing about the negative dichroic band at 210 mμ.

In view of these findings, a careful CD investigation of the optical properties of bridged lactones in solvents of different polarity is required before any correlation between sign of Cotton effects and molecular conformation can be made.[33,34,37,38]

Experimental Section

Circular dichroism spectra were obtained from a Cary 60 automatic recording spectropolarimeter equipped with a Cary CD attachment. A 450-W Osram xenon lamp was employed as the light source.

All melting points are uncorrected.

Solvents for Spectroscopic Studies.—Distilled water was employed for the aqueous measurements. Trifluoroethanol was purchased from Halocarbon, Inc.

Acetonitrile, isooctane, n-hexane, and methanol were Spectro Grade from either Fisher Scientific or Matheson Coleman and Bell. Trimethyl phosphate (Aldrich), hexafluoro-2-propanol

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(Aldrich), and hexafluoroacetone trihydrate (Hynes) were used without further purification. The latter was stored under refrigeration. Standard buffer solutions, pH 2.00 ± 0.02, 25° (potassium chloride–hydrochloric acid buffer), 0.05 M, and pH 9.00 ± 0.2, 25° (boric acid–potassium chloride–sodium hydroxide buffer), 0.1 M, were purchased from Fisher Scientific Co.

(S)-(+)-Lactic acid and (R)-(−)-lactic acid, 100%, were purchased from Mann Research Laboratory.

(R)-(−)-Mandelic acid, mp 132–134°, [α]D −155 ±5° (c 5, water), was purchased from Fluka AG.

(S,S)-3,6-Dimethyl-1,4-dioxane-2,5-dione [(S,S)-Lactide] (I). —The (S,S)-lactide was prepared according to the method of Carothers, et al.:[39] mp 98.7°; [α]²⁵D +298° {lit.[40] mp 98.7°; [α]D −298° (for the [R,R]-lactide)}.

(R,R)-3,6-Diphenyl-1,4-dioxane-2,5-dione [(R,R)-Diphenylglycolide] (II). —A modified procedure of Schoberl and Wiehler[41] using naturally occurring (R)-(−)-mandelic acid[42] was used.

The crude glycolide was recrystallized from dioxane repeatedly to give 4 g (9.07%) of white crystals: mp 285–286°; [α]²⁶D +91.2° (c 1, dimethylformamide).

1,8,8-Trimethyl-3-oxabicyclo[3.2.1]octan-2-one (α-Campholide) (III). —α-Campholide was prepared according to the method of Salmon–Legagneur:[43] mp 208–218°; [α]²⁵D −21.0° (c

0.5317, gram/milliliter in ethanol) {lit. mp 209.5–211.5°,[44] 210–211°;[45] [α]D −20° [46] (ethanol)}.

Methyl (R)-Mandelate.—(R)-Mandelic acid (10 g, 0.066 mol) and methanol (5.3 ml, 0.132 mol) were dissolved in 50 ml of dry benzene containing 0.1 ml of concentrated sulfuric acid. The reaction mixture was refluxed for 3 hr, during which water was removed azeotropically using a Dean–Stark trap. The reaction mixture was allowed to cool and was then extracted three times with 50-ml portions of a saturated sodium bicarbonate solution. The aqueous layer was then washed three times with 50-ml portions of ether. The combined ether and benzene solutions were dried over anhydrous magnesium sulfate and evaporated under reduced pressure. The resultant yellow oil was vacuum distilled (85° at 1.5 mm) to give a colorless liquid which solidified on cooling. The white solid was recrystallized from petroleum ether to give 9.3 g (85%) of a white crystalline material: mp 57–58°; [α]²⁵D −128.6° (c 1, ethanol).

Anal. Calcd for $C_9H_{10}O_3$: C, 65.05; H, 6.07. Found: C, 65.32; H, 5.95.

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Homogeneous Metalation of Alkylbenzenes

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Metalations of benzene, toluene, ethylbenzene, cumene, *t*-butylbenzene, and anisole, using *n*-butyllithium in conjunction with N,N,N',N'-tetramethylethylenediamine, were compared. Rearrangement of the kinetically favored products was *not* significant within the time periods used in this study. The extent of ring metalation, compared with benzylic metalation, follows the order toluene < ethylbenzene < cumene. Metalation at *ortho* positions is less extensive than at either *meta* or *para* positions in all cases. The ratio of *meta/para* derivatives was statistical (2:1) from metalation of ethylbenzene, cumene, and *t*-butylbenzene. Competitive metalation of benzene–alkylbenzene mixtures showed an order of benzylic reactivity of 6:1:0.1 for toluene/ethylbenzene/cumene, relative to benzene. The *ortho* positions of all alkylbenzenes underwent reaction less readily than that of benzene. Little difference was observed between the reactivities of either *meta* or *para* positions of alkylbenzenes and those of benzene. Competitive metalation of a benzene–anisole mixture shows that the *ortho* position of anisole undergoes metalation *ca.* 10² times faster than that of benzene. These observations are compared with those of metalations with alkylsodium and -potassium reagents and of base-catalyzed isotopic exchange studies involving the same substrates.

Metalation of alkylbenzenes, using organosodium and -potassium compounds, has received considerable attention in the chemical literature, resulting in a variety of mechanistic interpretations.[1] In recent years it has become rather commonly accepted that these reactions involve proton-abstraction processes.[1b,c,2] This conclusion is based primarily on the observation of rather large primary isotope effects[3] and comparison of metalation reactions with base-catalyzed isotopic exchange.[4] Recently, very extensive advances have been made in

the area of base-catalyzed exchange of hydrocarbons by such workers as Shatenshtein,[4] Streitwieser,[5] and the Esso research group.[6] A very important contribution to the task of understanding metalation systems was the observation that homogeneous reaction could be effected using *n*-butyllithium in conjunction with N,N,N',N'-tetramethylethylenediamine (TMEDA).[7,8]

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(8) The term homogeneous describes the fact that solid materials are not present. The state of aggregation of the various organometallic species is not known.