exchange rates to eq 25. For each of the other exchange reactions (Tables VIII and X), it was assumed that the exchange was first order in each component and an analogous kinetic treatment was applied. This assumption concerning the kinetic order clearly has no influence on the values of E_a reported in these tables; it does however influence the values of A. Consequently, the values of A for exchange reactions in solutions containing DME or tetramethylethylenediamine might be in error by some factor related to the concentrations and exponents in eq 25; this factor should not exceed 10^2. Attempts to obtain activation parameters for exchange of methylcyclopentadienylmagnesium and dicyclopentadienylmagnesium yielded an Arrhenius plot with a positive curvature. The reason for this behavior was not investigated.

Registry No.—CH_3MgBr, 75-16-1; CH_3MgI, 917-64-6; $(CH_3)_2Mg$, 2999-74-8; CH_3Li, 917-54-4; $(CH_3)_2Hg$, 593-74-8; LiBr, 7550-35-8; $MgBr_2$, 7789-48-2; $CH_3MgOC(CH_3)(CH_2CH_3)_2$, 13132-19-9; $[(CH_3CH_2)_2C(CH_3)O]_2Mg$, 13132-20-2; $(CH_3MgO)(CH_3)$-1,1-C_6H_{11}, 13132-21-3; PhMgBr, 100-58-3; Ph_2Mg, 555-54-4; $(C_5H_5)_2Fe$, 102-54-5; **9**, 4469-61-8; $(CH_3)_3CCH_2MgCl$, 13132-23-5; $(CH_3)_2Mg$, 557-18-6.

The Absolute Configurations of Some α-Thio Ethers Derived from Mandelic Acid

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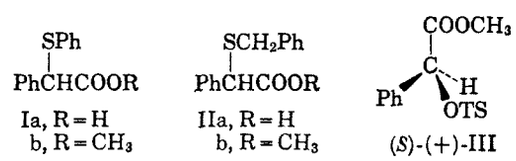
This research concerns establishment of the absolute configurations of (+)-α-phenylmercaptophenylacetic acid [(+)-Ia] and the enantiomers of α-benzylmercaptophenylacetic acid (IIa), the preparations and resolutions of which are described. Methyl (*S*)(+)-mandelate was converted to its O-tosylate [(*S*)(+)-III] and the latter was subjected to nucleophilic displacement reactions with phenylmercaptide and benzylmercaptide ions, respectively. The corresponding levorotatory α-thio ether esters, (−)-Ib and (−)-IIb, were obtained in 94 and 89% optical purity. These displacement reactions were then followed polarimetrically and found to exhibit clean-cut, second-order kinetic behavior, displacement by $PhCH_2S^-$ being about 3.5 times as rapid as by PhS^-. The straightforward SN2 nature of these displacements indicates unambiguously that the levorotatory α-thio ethers obtained possess the (*R*) configuration.

In connection with another problem to be described subsequently, we became interested in the absolute configurations of the enantiomers of α-phenylmercapto- (Ia) and α-benzylmercaptophenylacetic acid (IIa), each of which is readily derivable from mandelic acid. Compound Ia, mp 101–102°, has been prepared



by heating a mixture of mandelic acid and thiophenol[1,2] and has been resolved into its (+) enantiomer, $[\alpha]^{18}D$ +216°, using brucine.[1,3] Compound IIa, mp 95–96°, has been obtained previously by the action of benzyl bromide on α-mercaptophenylacetic acid, prepared in turn by hydrolysis of the O-ethylxanthate derived from α-bromophenylacetic acid.[4] We have now obtained IIa by a more direct route, namely, hydrolysis of the methyl ester IIb obtained by the action of sodium benzylmercaptide on racemic methyl α-chlorophenylacetate. Compound IIa could be readily resolved into its (+) enantiomer, mp 91–91.5°, $[\alpha]^{25}D$ +161°, and (−) enantiomer, mp 91.5–92°, $[\alpha]^{25}D$ −161°, using, in successive stages, the enantiomeric α-phenylethylamines.

The problem of the absolute configurations of (+)-Ia and the enantiomers of IIa was approached by means of displacement reactions on methyl O-tosyl-(*S*)(+)-mandelate [(*S*)(+)-III], using phenylmercaptide and benzylmercaptide ions, respectively, as nucleophiles. (*S*)(+)-III, mp 61–61.5°, $[\alpha]^{25}D$ +67.2°, was readily obtained by the action of *p*-toluenesulfonyl chloride on methyl (*S*)(+)-mandelate in the presence of silver oxide. The action of PhS^- on (*S*)(+)-III afforded the ester (−)-Ib which was 94% optically pure [97% (−)-Ib, 3% (+)-Ib], while $PhCH_2S^-$ yielded ester (−)-IIb of about 89% optical purity. These displacements of (*S*)(+)-III were thus attended by a gratifyingly small degree of racemization.

In the absence of neighboring-group participation,[5,6] nucleophilic displacements of sulfonate esters are generally considered to be attended by inversion of configuration[7-9] and the specific assumption of an SN2 mechanism in sulfonate displacements by mercaptide ions has frequently been made.[10,11] Kenyon and coworkers,[12] using optical rotatory trends as criteria, concluded however that, while inversion is the usual path, some sulfonate esters may in fact react with certain nucleophiles (*e.g.*, ammonia, piperidine, *p*-toluidine) with retention of configuration. Moreover, since kinetic criteria have apparently never been sought for the displacement of tosylate groups by mercaptide nucleophiles, we thought it therefore desirable to establish the mechanism of the above displacement reactions of (*S*)(+)-III by kinetic measurements.

The reaction of (*S*)(+)-III with sodium benzylmer-

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(12) J. Kenyon, H. Phillips, and V. P. Pittman, *J. Chem. Soc.*, 1072 (1935).

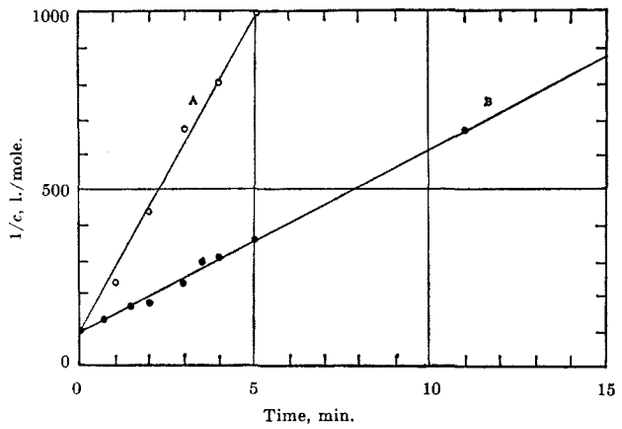


Figure 1.—Second-order rate plot for the reaction of methyl O-tosyl-(*S*)(+)-mandelate (0.01 *M*) with sodium benzylmercaptide (A, 0.01 *M*) and sodium phenylmercaptide (B, 0.01 *M*).

captide, each at 0.01 *M* concentration in 95:5 EtOH–$PhCH_2SH$ solvent, was followed polarimetrically, observing optical rotation as a function of time. The reaction proved extremely rapid ($t_{1/2}$ *ca.* 0.6 min) and a subsequent plot of $1/c$ *vs.* t produced a straight line (Figure 1A) whose slope indicated a second-order rate constant[13] of about 176 l./mole min. An attempt was made to investigate these second-order kinetics further by doubling individually the concentrations of both (*S*)(+)-III and PCH_2S^-. The results were qualitatively in accord with second-order behavior ($t_{1/2}$ *ca.* 0.3 min), but the reaction was too rapid to permit accurate polarimetric observations.

The above experiments were repeated using (*S*)(+)-III and sodium phenylmercaptide, each 0.01 *M* in 95:5 EtOH–PhSH solvent. A plot of $1/c$ *vs.* t again afforded a straight line (Figure 1B) whose slope gave a second-order rate constant of 51 l./mole min. The latter experiment was then repeated individually doubling the concentrations of both (*S*)(+)-III and PhS^-, whereupon a plot of log $[a(b - x)/b(a - x)]$ *vs.* t gave a straight line (Figure 2) whose slope again corresponded[14] to k = 49 l./mole min. The SN2 displacement of tosylate ion from (*S*)(+)-III is thus about 3.5 times as rapid with benzylmercaptide as with phenylmercaptide ion. (*S*)(+)-III proved optically stable in the solvents used (5% $PhCH_2SH$ and PhSH, respectively, in ethanol), indicating that these mercaptans themselves were ineffective nucleophiles under our reaction conditions.

As described in the Experimental Section, crystalline amide derivatives of many of the above optically active compounds were prepared for purposes of additional characterization and racemic counterparts of all compounds were obtained during exploratory pilot syntheses. The above kinetic experiments were employed to estimate suitable reaction conditions for the mercaptide displacements of (*S*)(+)-III on a preparative scale.

The clean-cut second-order kinetics observed in the above mercaptide displacements on (*S*)(+)-III indicate that the levorotory α-thio ethers obtained have the (*R*) absolute configuration (IV) and their high optical purity argues for 94–97% inversion of configuration during their preparation from (*S*)(+)-III.

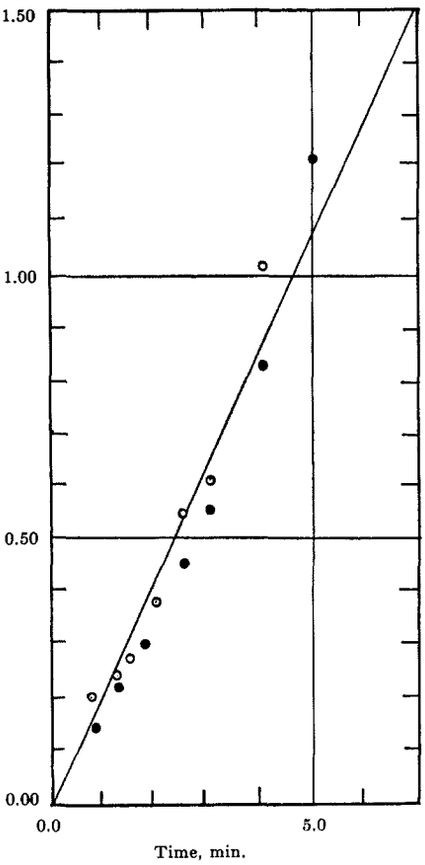
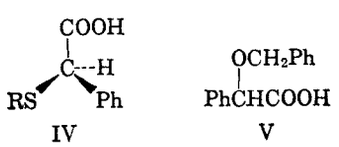


Figure 2.—Second-order rate plot for the reaction of methyl O-tolyl-(*S*)(+)-mandelate (O, 0.01 *M*; ●, 0.02 *M*) with sodium phenylmercaptide (O, 0.02 *M*; ●, 0.01 *M*).



Another aspect of the present study involved the configurations of the previously undescribed enantiomers of O-benzylmandelic acid (V). Racemic V, mp 61.5–63°, was prepared by the action of benzyl bromide and silver oxide on methyl mandelate, followed by hydrolysis of the resulting O-benzyl ester. When the same reaction sequence was applied to methyl (*R*)(−)-mandelate, syrupy O-benzyl-(*R*)(−)-mandelic acid was formed in about 90% optical purity. The pure product $[\alpha]^{25}D$ −119°, was obtained by additional resolution with (+)-α-phenylethylamine. When an attempt was made to prepare methyl O-benzyl-(*R*)-(−)-mandelate by the action of 1 equiv of sodium benzylate in benzyl alcohol on (*S*)(+)-III, however, "instantaneous" racemization was observed polarimetrically and only racemic V was isolable on subsequent hydrolysis. This displacement therefore could not be studied kinetically. Racemic V, mp 158–160°, has recently been claimed by Norula and Kenyon[15] to result as a by-product of the action of sodium ethoxide on the levorotatory benzhydryl ether of ethyl mandelate. Their structural assignments,

(13) A. A. Frost and R. G. Pearson, "Kinetics and Mechanism," John Wiley and Sons, Inc., New York, N. Y., 1953, p 13.

(14) F. H. Getman and F. Daniels, "Outlines of Theoretical Chemistry," 6th ed, John Wiley and Sons, Inc., New York, N. Y., 1937, p 323.

(15) J. L. Norula and J. Kenyon, *Current Sci.* (India), **32**, 14 (1963); *Chem. Abstr.*, **59**, 2684*g* (1963).

however, are supported by neither analytical nor additional structural data. Our structure of V is attested by two unambiguous synthetic routes, its preparation in enantiomerically pure form, its conversion both as racemate and enantiomer into additional crystalline derivatives (amides), and its nmr spectrum (*cf.* Experimental Section).

Experimental Section

α-Benzylmercaptophenylacetic Acid (IIa).—Methyl mandelate (32.20 g, 0.194 mole) was dissolved in chloroform (40 ml) and the solution was chilled in ice and treated with phosphorous pentachloride (46.5 g, 0.223 mole) over a 15-min period with magnetic stirring. The mixture was stirred at room temperature for 2 hr, diluted with additional chloroform (40 ml), and then poured slowly into 500 ml of ice water. The layers were separated and the aqueous layer was extracted once with chloroform. The chloroform layers were washed twice with ice water, then with cold sodium bicarbonate solution until gas evolution ceased, and then dried over anhyrous magnesium sulfate and filtered. The volume was adjusted to 150 ml with chloroform and the solution was poured slowly into a solution of sodium (4.19 g, 0.213 g-atom) in absolute ethanol (150 ml) containing benzyl mercaptan (26.41 g, 0.213 mole). A precipitate formed almost immediately, considerable heat was evolved, and the solution was cooled slightly during the addition. The mixture was heated under reflux for 90 min, then allowed to stand overnight, and finally evaporated approximately to dryness under vacuum in a rotary evaporator. The residue was treated with ether and water and the water layer was extracted with ether. The combined ether layers were washed with water, 5% aqueous potassium hydroxide, and water, then dried ($MgSO_4$), and filtered through Norit. The filtrate (still yellow) was stripped of ether to yield 44.24 g (83.8%) of crude methyl α-benzylmercaptophenylacetate, a yellow oil. This was treated with 10% aqueous sodium hydroxide (190 ml) and the mixture heated under reflux for 10 hr, cooled, and extracted three times with ether (discard). The aqueous layer was acidified with sulfuric acid, chilled, and extracted twice with ether. The ether extract was washed with water, dried ($MgSO_4$), filtered through Norit, and evaporated to yield 36.2 g (86%) of crude acidic product, an amber oil which crystallized on standing. A sample of this oil was recrystallized from a mixture of benzene and hexane, affording a pure crystalline product, mp 86°. Iskander and Tewfik[4] report a lengthier preparation of racemic α-benzylmercaptophenylacetic acid, mp 85-86°.

The nmr spectrum of the above acid (tetramethylsilane internal standard, Varian A-60 spectrometer, $CDCl_3$ solvent) showed the carboxyl proton at 9.45 ppm, phenyl protons between 7.1 and 7.5 ppm, the CH proton at 4.40 ppm, and the CH_2 protons as a pair of doublets located at 3.80 and 3.67 ppm (coupling constant 14 Hz).

α-Benzylmercaptophenylacetamide.—The above acid (1.00 g) was dissolved in benzene (3 ml) and thionyl chloride (5 ml) and the mixture was heated under reflux for 30 min. The solvents were evaporated, the residue was treated with benzene (5 ml), and the solvent was again stripped in a rotary evaporator. The residue was dissolved in ether (5 ml) and shaken vigorously with ice cold ammonium hydroxide (25 ml). The solid was filtered and the ether layer of the filtrate evaporated to dryness. The combined crude amide product, 1.05 g (105%), was recrystallized twice from a mixture of chloroform (10 ml) and hexane (20 ml), affording a pure sample, mp 136.5–137°.

Anal. Calcd for $C_{15}H_{15}NOS$: C, 70.00; H, 5.87; M, 5.44; S, 12.46. Found: C, 70.32; H, 5.94; N, 5.16; S, 12.23.

Resolution of α-Benzylmercaptophenylacetic Acid.—The above crude acid (33.54 g) was dissolved in hot ethanol (100 ml) and treated with (−)-α-phenylethylamine (15.76 g). After 2 hr, 24.37 g of salt crystallized, $[\alpha]^{25}D$ + 59° (*c* 1.43, EtOH). This material was recrystallized from hot ethanol (75 ml), cooling slowly for 1.5 hr, to yield 17.48 g of salt, $[\alpha]^{25}D$ +111° (*c* 1.32, EtOH). Another recrystallization from ethanol (80 ml) afforded 13.30 g, $[\alpha]^{25}D$ +136° (*c* 1.47, EtOH). Two additional recrystallizations produced what appeared to be optically pure (−)-α-phenylethylammonium (+)-α-benzylmercaptophenylacetate, long needles, 9.76 g, mp 156.5–157.5°, $[\alpha]^{25}D$ +144° (*c* 1.88, EtOH).

Anal. Calcd for $C_{23}H_{25}NO_2S$: C, 72.78; H, 6.64. Found: C, 72.57; H, 6.58.

The above pure salt (9.40 g) was decomposed with dilute sulfuric acid, followed by extraction with ether. Customary processing afforded 6.47 g (101%) of thick colorless oil which crystallized on standing, $[\alpha]^{25}D$ +161° (*c* 0.97, EtOH). The product was recrystallized from a mixture of benzene (12 ml) and hexane (30 ml) to yield 5.70 g of pure (*S*)(+)-α-benzylmercaptophenylacetic acid [(*S*)(+)-IIa], mp 91–91.5°, $[\alpha]^{25}D$ +161° (*c* 0.89, EtOH).

Anal. Calcd for $C_{15}H_{14}O_2S$: C, 69.74; H, 5.46; S, 12.41. Found: C, 69.77; H, 5.48; S, 12.28.

From the mother liquors the unresolved acid was recovered in a similar manner, 30.49 g (91%). A portion of this (24.02 g) was dissolved in hot ethanol (70 ml) and treated with (+)-α-phenylethylamine (11.26 g). On standing at room temperature for 4 hr, 19.02 g of salt crystallized, $[\alpha]^{25}D$ −122.5° (*c* 1.23, EtOH). Another recrystallization from ethaol (80 ml) afforded 15.90 g of salt having $[\alpha]^{25}D$ −141.8° (*c* 1.42, EtOH). A third recrystallization from ethanol yielded 13.51 g of (+)-α-phenylethylammonium (−)-α-benzylmercaptophenylacetate, mp 156–156.5°, $[\alpha]^{25}D$ −142° (*c* 1.30, EtOH).

Anal. Calcd for $C_{23}H_{25}NO_2S$: C, 72.78; H, 6.64. Found: C, 72.52; H, 6.65.

The above salt (13.05 g) was decomposed as before and the crude syrupy product (8.90 g, 100%), which quickly crystallized, was recrystallized from benzene (16 ml) and hexane (40 ml), yielding pure (*R*)(−)-α-benzylmercaptophenylacetic acid [(*R*)-(−)-IIa], mp 91.5–92°, $[\alpha]^{25}D$ −161° (*c* 1.65, EtOH).

Anal. Calcd for $C_{15}H_{14}O_2S$: C, 69.74; H, 5.46; S, 12.41. Found: C, 69.89; H, 5.34; S, 12.40.

(*S*)(+)- and (*R*)(−)-α-Benzylmercaptophenylacetamide.—The above (*S*)(+) acid was converted to its amide using thionyl chloride as described for the conversion of the above racemic acid. The crude product (92.4%) had mp 164.5–166° and was recrystallized (Norit) from a mixture of acetone and hexane. The pure product had mp 170–170.5° and $[\alpha]^{25}D$ +160° (*c* 0.78, acetone).

Anal. Calcd for $C_{15}H_{15}NOS$: C, 70.00; H, 5.87. Found: C, 69.98; H, 6.01.

In exactly the same manner, the above (*R*)(−)-α-benzylmercaptophenylacetic acid was converted into its amide, mp 169–170°, $[\alpha]^{25}D$ −156° (*c* 0.53, acetone).

Anal. Calcd for $C_{15}H_{15}NOS$: C, 70.00; H, 5.87. Found: C, 70.35; H, 6.00.

Methyl (*R*)(−)-α-Benzylmercaptophenylacetate [(*R*)(−)-IIb].—The above (*R*)(−) acid (1.29 g) in absolute methanol (15 ml) was treated with sulfuric acid (0.5 ml) and the mixture was heated under reflux for 5 hr, then cooled and poured into ice water (150 ml). Extraction with ether, washing of the extract with 5% aqueous sodium hydroxide, drying ($MgSO_4$), and solvent evaporation afforded 1.27 g (93.3%) of the desired ester, a clear oil which was homogeneous on thin layer chromatography, $n^{18}D$ 1.5862, $[\alpha]^{25}D$ −143° (*c* 2.73, EtOH).

Anal. Calcd for $C_{16}H_{16}O_2S$: C, 70.56; H, 5.92. Found: C, 70.33; H, 5.80.

Methyl O-Tosylmandelate.—A mixture of methyl mandelate (3.00 g) *p*-toluenesulfonyl chloride (3.79 g, 10% excess), silver oxide (15 g), anhydrous magnesium sulfate (10 g), and glass beads (20 g) in *n*-butyl ether (50 ml) was stirred vigorously ($CaCl_2$ tube) on the steam bath for 22 hr, then cooled, diluted with ether, and filtered (Celite). The solvents were distilled from the filtrate by rotary vacuum evaporation at 100°, resulting in 3.90 g (67.5%) of mobile oil which crystallized on standing, mp 71–74°. The crude product was recrystallized twice from ethanol, affording 2.47 g of pure tosylate, mp 89.5–90°.

Anal. Calcd for $C_{16}H_{16}O_5S$: C, 59.98; H, 5.03; S, 10.01. Found: C, 59.80; H, 4.94; S, 9.83.

Methyl O-Tosyl-(*S*)(+)-mandelate [(*S*)(+)-III].—Methyl (*S*)(+)-mandelate (6.12 g, $[\alpha]^{25}D$ +170° (*c* 1.93, $CHCl_3$), 97.6% optically pure[16]) *p*-toluenesulfonyl chloride (7.73 g), silver oxide (31 g), anhydrous magnesium sulfate (20 g), and glass beads (40 g) in *n*-butyl ether (150 ml) were stirred vigorously as above on the steam bath for 19 hr. Analogous processing yielded 9.33 g (79.1%) of crude amber oil which crystallized on standing. This was recrystallized from ethanol (40 ml) to give 5.60 g of product, mp 61–61.5°, $[\alpha]^{25}D$ +67.0° (*c* 0.91, EtOH). A second recrystal-

(16) W. A. Bonner, *J. Am. Chem. Soc.*, **73**, 3131 (1951).

lization afforded pure methyl O-tosyl-(*S*)(+)-mandelate, mp 61–61.5°, $[\alpha]^{25}D$ +67.2° (*c* 1.25, EtOH).

Anal. Calcd for $C_{16}H_{16}O_5S$: C, 59.98; H, 5.03; S, 10.01. Found: C, 59.78; H, 5.00; S, 9.94.

Methyl O-Tosyl-(*S*)(+)-mandelate and Sodium Benzylmercaptide.—A solution of sodium ethoxide (0.02 g of Na/ml) was made by dissolving sodium (0.50 g) in absolute ethanol (25 ml). This solution was also employed in each of the kinetic experiments described below. This solution (3.60 ml) (containing 0.072 g of Na, 1 equiv) was added to absolute ethanol (11.4 ml) and the mixture treated with benzylmercaptan (1.0 ml, 2.72 equiv). The solution was added to the above (*S*)(+)-III (1.00 g), causing immediate spontaneous warming and precipitation of sodium tosylate. The mixture was heated on the steam bath for 15 min, cooled, and filtered, whereupon the filtrate had an optical rotation of −7.14°/dm. The filtrate was heated on the steam bath for an additional 15 min and cooled, whereupon the rotation was −7.25°/dm. Heating on the steam bath for an additional 30 min engendered no further increase in rotation and the mixture was poured into ice water (150 ml), treated with salt, and extracted three times with ether. The extracts were washed once with cold 10% aqueous sodium hydroxide, dried over anhydrous magnesium sulfate, filtered, and evaporated to yield 0.85 g (100%) of a thin oil smelling faintly of benzylmercaptan. Thin layer chromatography showed one large spot with an R_f identical with that of the above methyl (*R*)(−)-α-benzylmercaptophenylacetate, plus one very small additional spot with a higher R_f. The crude product, $[\alpha]^{25}D$ −125° (*c* 2.46, EtOH), was steam distilled (50–75 ml) until the odor of benzylmercaptan was removed and the residue was extracted with ether as before. The dried extract was filtered through Norit and stripped of solvent to yield 0.74 g (87%) of thin, odorless oil (*R*)(−)-IIb, $[\alpha]^{25}D$ −128° (*c* 2.55, EtOH), which still showed a very small amount of higher R_f impurity on thin chromatography. The infrared spectrum of this product was identical in all respects with that of the authentic optically pure methyl (*R*)(−)-α-benzylmercaptophenylacetate above. The optical rotation of the product indicates it to be 89% optically pure and the kinetic experiments below indicate that the tosylate displacement was attended by Walden inversion.

Methyl O-Tosyl-(*S*)(+)-mandelate and Sodium Phenyl Phenylmercaptide.—The above (*S*)(+)-III (0.32 g) in warm absolute ethanol (3 ml) was treated with a solution of the above sodium ethoxide solution (1.15 ml; 0.023 g of Na, 1 equiv) in absolute ethanol (3.85 ml) containing thiophenol (0.51 ml, 5 equiv). Precipitation of sodium tosylate was almost instantaneous. The mixture was allowed to stand at room temperature for 1 hr, then heated on the steam bath for 10 min, cooled, filtered, and poured into ice water (50 ml) containing salt. The product was extracted with ether as before and the extract washed with 10% aqueous sodium hydroxide, dried, filtered, and stripped of solvent to yield 0.246 g (95.3%) of clear, odorless oil (*R*)(−)-Ib, $[\alpha]^{25}D$ −128° (*c* 3.18, EtOH). The infrared spectrum of this product was identical in all respects with the enantiomeric methyl (*S*)(+)-α-phenylmercaptophenylacetate described below. Thin layer chromatography showed the present product and the authentic sample to have identical R_f values and the present product again to have an insignificant amount of a higher R_f component. On the basis of its optical rotation, the present product appears to be 94% optically pure.

In an earlier experiment the crude methyl (*R*)(−)-α-phenylmercaptophenylacetate product was subjected to acid hydrolysis. After one crystallization, the crude (*R*)(−)-α-phenylmercaptophenylacetic acid [(*R*)(−)-Ia] obtained had $[\alpha]^{25}D$ −183° (*c* 0.33, 1:1 $CHCl_3$–EtOH) and mp 122.5–125°. Its infrared spectrum was identical in all respects with that of the authentic racemic material.

Anal. Calcd for $C_{14}H_{12}O_2S$: C, 68.82; H, 4.95; S, 13.13. Found: C, 68.50; H, 4.84; S, 12.19.

Methyl (*S*)(+)-α-Phenylmercaptophenylacetate [(*S*)(+)-Ib].—A previously prepared sample of (*S*)(+)-α-phenylmercaptophenylacetic acid[1] (51 mg, mp 125–127°, $[\alpha]^{25}D$ +200° (1:1 $CHCl_3$–EtOH), 93% optically pure) was dissolved in methanol (5 ml) and treated with sulfuric acid (0.2 ml). The mixture was heated under reflux for 5 hr and the ester product isolated in the usual way: 49 mg (90.7%) of a clear, thin oil; $[\alpha]^{25}D$ +126° (*c* 1.53, EtOH).

Anal. Calcd for $C_{15}H_{14}O_2S$: C, 69.74; H, 5.46. Found: C, 69.66; H, 5.52.

Based on the optical purity of the starting acid (93%),[3] calculations indicate $[\alpha]^{25}D$ +136° for the rotation of the optically pure ester.

Methyl O-Tosyl-(*S*)(+)-mandelate with Sodium Benzyloxide.—The above (*S*)(+)-III (1.000 g) was dissolved in benzyl alcohol (15 ml) and the solution was treated with 3.59 ml (containing 0.0719 g of Na, 1 equiv) of a solution of sodium (0.50 g) in benzyl alcohol (25.0 ml). The optical rotation of the mixture was 0.0°/dm and the solution began clouding up with sodium tosylate after standing about 1 min. The mixture was heated on the steam bath for 1 hr and filtered; the filtrate again proved optically inactive. Optical inactivity persisted after heating an additional 45 min. To check these results, the tosylate (0.10 g) was dissolved in benzyl alcohol (3 ml), giving a solution which had a rotation of +2.58°/dm. The solution was treated with 0.36 ml (1 equiv) of the above sodium benzyloxide solution and the resulting mixture was found to be optically inactive before its rotation could be measured (less than 1 min). The solution began clouding up with sodium tosylate after 2 min. Thus the displacement reaction and racemization appear to be "instantaneous" on a mole to mole basis of reactants.

The original reaction mixture was distilled in a small Claisen flask to remove excess benzyl alcohol (bp 62–66° (0.1 mm)), until the residue was approximately 2 ml. The residue was dissolved in dioxane (10 ml) and the mixture was treated with water (25 ml) containing sulfuric acid (2 ml). The solution was heated under reflux for 18 hr to effect hydrolysis and the product was isolated in the usual way. The crude acid obtained weighed 0.33 g (43.6%), proved to be optically inactive, crystallized on seeding with the authentic O-benzylmandelic acid described below, and showed an infrared spectrum identical with the latter. To test if (*S*)(+)-III was solvolized in benzyl alcohol lacking sodium benzyloxide, 0.05 g of the tosylate was dissolved in 3 ml of benzyl alcohol. The solution showed an optical rotation of 1.24°/dm, unchanged after 19 hr.

Displacement Rates of Methyl O-Tosyl-(*S*)(+)-mandelate. A. With Sodium Benzylmercaptide.—The solvent employed was a 5% solution (by volume) of benzylmercaptan in absolute ethanol. (*S*)(+)-III (32.0 mg, 0.1 mmole) was dissolved in 10 ml of solvent, making a 0.01 *M* solution which showed a rotation of 0.41°/2 dm, unchanged after 24 hr. This rotation was employed for the value at t_0.

Solutions of (*S*)(+)-III (0.01 *M*) and Sodium Benzylmercaptide (0.01 *M*).—(*S*)(+)-III (1 mmole) was dissolved in 5.00 ml of solvent. The above sodium ethoxide solution (containing 0.02 g of Na/ml; 0.115 ml, 0.0023 g of Na) was added to solvent and the mixture was made up to 5.00 ml with additional solvent. The two reaction solutions were mixed rapidly at t_0 and placed in a 2-dm side-filling polarimeter tube as quickly as possible, and optical rotation measurements as a function of time were made as follows (*t*, min; α, deg/2 dm): 1.1, −0.30; 2.0, −0.51; 3.0, −0.61; 4.0, −0.64; 5.0, −0.67; 10.0, −0.75; 21.0, −0.79 (constant).

From a straight-line plot of percentage composition *vs.* optical rotation (100% tosylate, α_0 +0.41°; 100% product, α_∞ −0.79°), the concentration of tosylate was calculated at each time value. The second-order kinetics of the reaction were shown (Figure 1) by the linear plot of the reciprocal of tosylate concentration *vs.* time. The slope of the resulting line gives a value of 176 l./mole min for the specific rate constant of this reaction, corresponding to a half-life of 0.6 min. Attempts were made to study the rate increase occasioned by doubling the concentrations each of the tosylate and sodium benzylmercaptide. The results were qualitatively in accord with the predictions of second-order kinetics, but the reactions were too fast to follow accurately polarimetrically.

B. With Sodium Phenylmercaptide.—The solvent employed was a 5% (by volume) solution of thiophenol in absolute ethanol. A 0.01 *M* solution of (*S*)(+)-III (32.0 mg) dissolved to 10.0 ml in the solvent had a rotation of 0.40°/2 dm (used for α_0), unchanged after 100 min.

(*S*)(+)-III (0.01 *M*) and Sodium Phenylmercaptide (0.01 *M*).—Tosylate (32.0 mg) was dissolved in solvent (5.00 ml). The above sodium ethoxide solution (0.115 ml, 1 equiv) was diluted to the 5.00-ml mark with solvent. The two solutions were mixed at t_0, poured into the previous 2-dm polarimeter tube, and rotations were observed at the indicated times as follows (*t*, min; α, deg/2 dm): 0.75, +0.14; 1.50, −0.05; 2.0, −0.08; 3.0, −0.24; 3.5, −0.33; 4.0, −0.34; 5.0, −0.40; 11.0; −0.54;

18.0, −0.61; 36.0, −0.67; 53.0, −0.71 (constant). The reciprocal of concentration, estimated as described above, was plotted against time as before (Figure 1), giving a straight line whose slope indicated a specific rate constant of 51 l./mole min, corresponding to $t_{1/2}$ 1.95 min.

(*S*)(+)-III (0.01 *M*) and Sodium Phenylmercaptide (0.02 *M*).—To confirm the above second-order kinetics, variations were made in both tosylate and phenylmercaptide concentration. (*S*)(+)-III (32.0 mg) was dissolved in 5.00 ml of solvent. Sodium ethoxide solution (0.23 ml) was diluted to 5.00 ml with solvent. The solutions were mixed at t_0 and the following data observed (t, min; α, deg/2 dm): 0.75, −0.20; 1.25, −0.26; 1.50, −0.33; 2.0, −0.42; 2.5, −0.52; 3.0, −0.56; 4.0, −0.65, 5.0, −0.68; 10.0, −0.72 (constant).

(*S*)(+)-III (0.02 *M*) and Sodium Phenylmercaptide (0.01 *M*).—Tosylate (64.0 mg) was dissolved in 5.0 ml of solvent. The sodium ethoxide solution (0.115 ml) was diluted to 5.00 ml with solvent. The solutions were mixed at t_0 and the following data observed [t, min; (α − 0.40), deg/2 dm]: 0.8, −0.10; 1.25, −0.23; 1.75, −0.34; 2.5, −0.47; 3.0, −0.53; 4.0, −0.62; 5.0, −0.67; 6.0, −0.70; 13.0, −0.73. (constant). The quantity log $[a(b - x)/b(a - x)]$ for each of the rotation values in this and the previous experiment was estimated in a manner analogous to that described above. A plot of these values *vs.* time for the last two experiments (Figure 2) gave a reasonably straight line whose slope permitted the estimation of the specific rate constant as 49 l./mole min, in acceptable agreement with k for the original experiment with equimolar concentrations of reactants.

O-Benzylmandelic Acid (V).—A mixture of methyl mandelate (5.0 g), silver oxide (20 g), anhydrous magnesium sulfate (10 g), and the glass beads (15 g) in butyl ether (60 ml) containing benzyl bromide (25.8 g, 5 equiv) was heated on the steam bath under vigorous stirring in a flask equipped with a mercury-sealed stirrer, condenser, and calcium chloride tube. Heating was stopped after 8 hr and stirring was continued over night, whereupon the mixture was filtered and the cake rinsed with ether. The filtrate was steam distilled to remove solvents and unreacted benzyl bromide and the residue was treated with salt and extracted three times with ether. The extracts were washed with 5% aqueous potassium hydroxide, dried over anhydrous magnesium sulfate, decolorized by filtration through Norit, and stripped of solvent to produce 9.8 g of mobile amber oil. The latter was dissolved in dioxane (20 ml) and treated with water (50 ml) and concentrated sulfuric acid (3 ml). The mixture was heated under reflux for 6 hr, cooled, made alkaline, and extracted well with ether. The dried extracts were evaporated to yield 6.4 g of neutral material. The alkaline layer was acidified and extracted three times with ether and the extracts were washed with water, dried over magnesium sulfate, decolorized (Norit), and stripped of solvent to provide 4.6 g (63%) of syrupy product which crystallized on standing in a vacuum over P_2O_5 for several days. Attempts to recrystallize the product from a mixture of benzene and hexane resulted only in an oil. Accordingly, the recrystallization solution was decolorized again with Norit, stripped of solvent, and crystallized again by seeding. The solid acid was finely pulverized and dried over P_2O_5 (0.1 mm) prior to analysis, mp 61.5–63.5°.

Anal. Calcd for $C_{15}H_{14}O_3$: C, 74.36; H, 5.83. Found: C, 73.97; H, 5.74.

O-Benzyl-(*R*)(−)-mandelic Acid [(*R*)(−)-V].—Methyl (*R*)(−)-mandelate (3.00 g, mp 54–54.5°, $[\alpha]^{25}D$ −170° (*c* 0.74, $CHCl_3$), 97.6% optically pure),[16] silver oxide (15 g), anhydrous magnesium sulfate (8 g), and glass beads (12 g) in butyl ether (60 ml) containing benzyl bromide (13 ml) were heated on the steam bath under vigorous stirring for 8 hr as above, then stirred at room temperature for 4 hr. The crude ester was isolated as before as 7.45 g of thin amber oil, $[\alpha]^{25}D$ −30.1° (*c* 4.61, dioxane). Hydrolysis was attempted by heating the crude product with vigorous stirring in refluxing aqueous dioxane (same quantities as above) for 5 hr. The hydrolysate was processed as previously, yielding 4.58 g of a neutral fraction, $[\alpha]^{25}D$ −21.4° (*c* 4.77, $CHCl_3$), and 2.58 g (59%) of acidic product, a thick amber oil, $[\alpha]^{25}D$ −108° (*c* 2.40, $CHCl_3$), whose infrared spectrum was identical with that of the racemic acid above. The low yield of acid and high optical activity of the neutral fraction suggested that hydrolysis was incomplete. Accordingly, the 4.58 g of neutral product was again treated with acidified aqueous dioxane and stirred under reflux for an additional 15 hr. Similar processing afforded 3.40 g of neutral fraction and 0.68 g of additional acidic material, $[\alpha]^{25}D$ −109° (*c* 2.11, $CHCl_3$). The comparable rotations of the two acidic fractions indicate that racemization did not accompany the hydrolysis steps. The total yield was 3.26 g (74.6%).

The acid was then subjected to resolution to assess its optical purity. Acid (3.13 g) in ethanol (20 ml) was treated with (+)-α-phenylethylamine (1.57 g) and the solution was allowed to cool slowly to 25°, then chilled to 0°, and filtered, affording 3.27 g of phenylethylamine salt, mp 173.5–174.5°, $[\alpha]^{25}D$ −38.8° (*c* 1.39, EtOH). The salt was dissolved in hot ethanol (35 ml); the solution was evaporated to 18 ml and seeded, allowed to cool slowly to 25°, then chilled at 0° for several hours, and filtered, affording 3.09 g of salt, mp 175.5–176°, $[\alpha]^{25}D$ −38.9° (*c* 1.80, EtOH). The identical optical rotations of the two salt samples suggested optical homogeneity.

Anal. Calcd for $C_{23}H_{25}NO_3$: C, 76.00; H, 6.93; N, 3.85. Found: C, 75.79; H, 6.88; N, 3.68.

The above (+)-α-phenylethylammonium O-benzyl-(*R*)(−)-mandelate (3.04 g) was decomposed in water (60 ml) containing sulfuric acid (3 ml) and the mixture was extracted three times with ether. The extract was washed with water, dried over anhydrous magnesium sulfate, filtered, and stripped of solvent to yield 1.95 g (97.5%) of optically pure acid, a thick syrup having $[\alpha]^{25}D$ −119° (*c* 1.81, $CHCl_3$).

Anal. Calcd for $C_{15}H_{14}O_3$: C, 74.36; H, 5.83. Found: C, 73.75; H, 5.81.

The integrated nmr spectrum of this product (measured as before) showed one carboxyl proton at 11.0 ppm, ten phenyl protons between 7.1 and 7.5 ppm, one CH proton at 4.92 ppm, and two CH_2 protons at 4.53 ppm. From its optical rotation, the crude, unresolved O-benzyl-(*R*)(−)-mandelic acid obtained in the present preparation appeared to be 95% optically pure.

O-Benzyl-(*R*)(−)-mandelamide.—The above (*R*)(−) acid (0.35 g) was dissolved in ethanol (10 ml) and treated with a few drops of a 5% solution of phenolphthalein in ethanol. The solution was titrated to the phenolphthalein end point with aqueous sodium hydroxide and the neutral solution was evaporated to dryness in an air stream. The solid sodium salt residue was dried overnight over P_2O_5 (0.1 mm), $[\alpha]^{25}D$ −59.0° (*c* 0.41, H_2O). After the procedure of Adams and Ulich,[17] the above sodium salt (0.35 g) was added slowly with stirring to a solution of oxalyl chloride (0.25 g, 1.5 equiv) in benzene (5 ml) contained in a flame-dried flask. The mixture was then heated under reflux for 15 min ($CaCl_2$ tube), whereupon the solvent was stripped by rotary vacuum evaporation. An additional 5 ml of benzene was added to the residue and the mixture was reevaporated. The residue was treated with anhydrous ether (5 ml) and then shaken with chilled ammonium hydroxide (40 ml) for several minutes. The white solid produced was extracted into ether and the extract was washed with water, dried over anhydrous magnesium sulfate, decolorized byfil tration hrough Norit, and stripped of solvent, yielding 0.23 g (72%) of white solid, mp 108.5–112.5°. The crude product was recrystallized twice from a mixture of acetone (1 ml) and hexane (10 ml), whereupon the pure product had mp 130.5° and $[\alpha]^{25}D$ −83.3° (*c* 0.30, acetone).

Anal. Calcd for $C_{15}H_{15}NO_2$: C, 74.66; H, 6.27; N, 5.81. Found: C, 74.70; H, 6.36; N, 5.67.

O-Benzylmandelamide.—The above racemic O-benzylmandelic acid was converted to its amide in a manner exactly similar to that described in the previous experiment. The crude product was again recrystallized from mixtures of acetone and hexane and the pure product had mp 139–139.5°.

Anal. Calcd for $C_{15}H_{15}NO_2$: C, 74.66; H, 6.27; N, 5.81. Found: C, 74.95; H, 6.42; N, 5.58.

Registry No.—(*R*)(−)-Ia, 13136-48-6; (*R*)(−)-Ib, 13136-49-7; (*S*)(+)-Ib, 13136-50-0; (*S*)(+)-IIa, 13136-51-1; (*R*)(−)-IIa, 13136-52-2; (*R*)(−)-IIb, 13233-09-5; (*S*)(+)-III, 13136-53-3; (*R*)(··)-V, 13136-54-4; (−)-α-phenylethylammonium (+)-α-benzylmercaptophenylacetate, 13136-55-5; (+)-α-phenylethylammonium (−)-α-benzylmercaptophenylacetate, 13136-56-6; (*S*)(+)-α-benzylmercaptophenylacetamide, 13136-57-7; (*R*)(−)-α-benzylmercaptophenylacetamide, 13136-58-8

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(+)-α-phenylethylammonium O-benzyl-(*R*)(−)-mandelate, 13136-59-9; O-benzyl-(*R*)(−)-mandelamide, 13136-60-2.

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Solvent-Assisted Ullmann Ether Synthesis. Reactions of Dihydric Phenols

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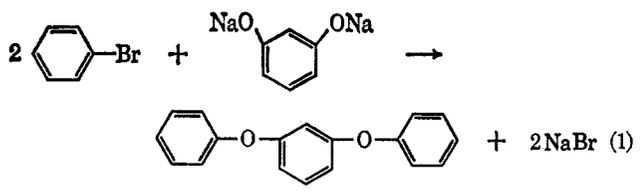
Certain organic solvents containing heteroatoms dissolve copper salts to form complexes which are catalytic in the Ullmann ether synthesis, thus allowing use of lower temperatures. When oxygen and water are excluded, salts of dihydric phenols can be allowed to react. By proper choice of solvent and conditions, the reaction can be directed toward polyphenyl ethers or phenolic ethers. Although resorcinol yields only tars under the usual melt conditions, the present system permits formation of *meta*-linked ethers in good yields. Rates of reaction of substituted bromobenzenes with disodium resorcinate in pyridine indicate nucleophilic attack by resorcinate dianion. Bromination of *m*-diphenoxybenzene under mild conditions led only to 2,4-diphenoxybromobenzene. This was condensed with various phenolic salts to synthesize a new class of nonlinear polyphenyl ethers

Although polyphenyl ethers are resistant to thermal, oxidative, and radiation damage,[1] their useful temperature range as fluids is restricted by the high melting points of the pure isomers. This problem is alleviated by employing mixtures of isomers, but liquid mixtures result only when a high proportion of the ether linkages are in the *meta* positions of the benzene rings.[2]

Low molecular weight polyphenyl ethers are usually prepared by the Ullmann ether synthesis.[3] Copper metal is the preferred catalyst and the phenate melt is exposed to air to convert the copper to an active form. When *meta*-linked ethers are sought, the synthesis of *m*-diphenoxybenzene illustrates the main problems encountered. The first choice is whether the middle ring shall be derived from *m*-dibromobenzene or from resorcinol. Pure *m*-dibromobenzene is not readily available and attempts to employ resorcinol directly in the Ullmann ether synthesis have been reported to yield only tars.[4,5] Failure to obtain polyphenyl ethers was ascribed to instability of the alkali metal salts of dihydric phenols at the temperature required for reaction.

Results and Discussion

With dry nitrogen to provide an inert atmosphere, cuprous chloride as catalyst, and pyridine as solvent, the disodium salt of resorcinol was converted to *m*-diphenoxybenzene in one step (eq 1). The yield of



recrystallized product was 70% (based on resorcinol). Details are given in experimental method A. The product is accompanied by a small yield of *m*-phenoxyphenol, which is an intermediate, as the sodium salt. The formation of *m*-phenoxyphenol and its further conversion were observed by gas chromatography during the course of the reaction. Oxygen must be rigorously excluded as it causes formation of tars at the expense of product. Phenolic salts, free of water and alcohol, are conveniently prepared from sodium methoxide. This reactant was used as described in method A for the preparation of all disalts except for those few cases where another method is specifically mentioned. An excess of base completely inhibits the reaction by destroying the copper catalyst. Reactions were therefore carried out by using only 95% of the theoretical quantity of base to make the disalt.

Solvent–Catalyst Interactions.—Successful solvents for the ether condensation must not only dissolve the reactants, but bring the copper catalyst into solution as well. Various cupric salts (chloride, bromide, sulfate, acetylacetonate) were catalytic when dissolved in solvents which brought them into solution with the formation of coordination complexes (Table I). Copper metal and cuprous oxide did not dissolve and did not promote the reaction. If copper acts as catalyst by forming a complex with the aryl bromide, it would appear that full coordination with solvent would be undesirable. Taking pyridine with cuprous chloride as

TABLE I

SOLVENTS IN THE PREPARATION OF *m*-DIPHENOXYBENZENE

Solvent for reaction at 125°	Yield from disodium resorcinate in 6 hr, %: *m*-Diphenoxybenzene	*m*-Phenoxyphenol
Pyridine (117°)	74	15
Pyridine + 2% water (112°)	4	22
2,4,6-Collidine	17	25
Pyridine N-oxide	18	40
Di-*n*-butylamine	32	19
1-Methyl-2-pyrrolidinone	11	46
Dimethylformamide	4	34
Hexamethylphosphoramide	5	47
Methyl sulfoxide	14	42
n-Propyl sulfone	42	33
Bis(2-methoxyethyl) ether	21	25

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