The Preparation, Resolution, and Absolute Configuration of α-Mercaptophenylacetic Acid

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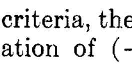
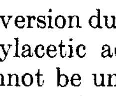
Received December 12, 1967

To resolve an ambiguity in the literature, kinetic and stereochemical experiments were undertaken to establish the absolute configuration of α-mercaptophenylacetic acid. Polarimetrically measured second-order rate constants for the reaction of hydrosulfide ion with methyl O-tosyl-(*S*)(+)-mandelate (IIb) showed a monotonic increase with time, suggesting formation of a strongly levototatory by-product. When the same reaction was conducted preparatively, the desired methyl (*R*)(−)-α-mercaptophenylacetate (IV) (68%) was isolated in about 44% optical purity, along with a by-product (32%), (−)-α,α′-di(carbomethoxy)dibenzyl sulfide (VI), of lower optical purity. S-(Thioncarboethoxy)-α-mercaptophenylacetic acid (VII), prepared by the action of potassium O-ethyldithiocarbonate on α-chlorophenylacetic acid, was hydrolyzed to yield racemic α-mercaptophenylacetic acid. This was resolved with the aid of cinchonidine, and the (−) enantiomer was obtained in about 80% optical purity. The latter substance was converted by the action of benzyl bromide and sodium bicarbonate into (*R*)(−)-α-benzylmercaptophenylacetic acid (Ie) of known absolute configuration, thus confirming the assignment of (−)-α-mercaptophenylacetic acid to the (*R*) series (Ia).

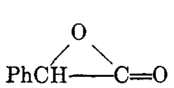
In 1927, while engaged in studies on the Walden inversion, Levene and coworkers[1] had occasion to prepare (+)-α-mercaptophenylacetic acid, (+)-PhCH(SH)-COOH {mp 80-87°, $[\alpha]^{20}_{\mathrm{D}}$ +71.5°, $[M]^{20}_{\mathrm{D}}$ +120.0° (ether); Na salt, $[\alpha]^{20}_{\mathrm{D}}$ +78.9°, $[M]^{20}_{\mathrm{D}}$ +149.9° (H_2O)} by the action of potassium hydrosulfide on (−)-α-bromophenylacetic acid {mp 87-88°, $[\alpha]^{20}_{\mathrm{D}}$ −104.6°, $[M]^{20}_{\mathrm{D}}$ −224.9° (ether); Na salt, $[\alpha]^{3}_{\mathrm{D}}$ −102.6°, $[M]^{3}_{\mathrm{D}}$ −243.1° (H_2O)}. Because the sodium salt of the (+)-α-mercaptophenylacetic acid was more dextrorotatory than was the free acid, Levene assigned it to the *d* series [(*R*) configuration], (Ia). Because the salt of the (−)-α-bromophenylacetic acid had a more levorotatory molecular rotation (albeit a more dextrorotatory specific rotation) than did the free acid Levene assigned this acid to the l series [(*S*) configuration] (IIa), and thereby concluded that Walden inversion had attended the conversion with KSH of the latter acid into the former. That Levene's simple optical comparisons were configurationally nondefinitive, however, was suggested by more recent findings that (−)-α-halogenophenylacetic acids actually possess the D [*i.e.*, (*R*)] configuration[2−6] (Ib) similar to (*R*)(−)-mandelic acid (Ic). Furthermore, in the absence of more definitive stereochemical or kinetic criteria, the occurrence of inversion during the transformation of (−)-α-bromophenylacetic acid into (+)-α-mercaptophenylacetic acid cannot be unequivocally assumed *a priori*. Since the reaction in question was conducted on free (−)-α-bromophenylacetic acid in the presence of a large excess of KSH, the reacting species was clearly the (−)-α-bromophenylacetate anion. Furthermore, since carboxylate anions may act as "configuration-retaining" neighboring groups *via* formation of intermediate α-lactones (III or its equivalent)[7,8] which both form with and react with inversion at C-α, there is therefore alternative precedent to postulate net configurational retention (*i.e.*, double inversion) in Levene's conversion of (−)-α-bromo- into (+)-α-mercaptophenylacetic acid. Thus, the questions of the absolute configuration of the latter acid and the presence or absence of net inversion in its reported formation from (−)-α-bromophenylacetic acid remain open ones, since all other studies of α-mercaptophenylacetic acid prior to and following that of Levene have involved only the racemic form.[9−12]



Ia, X = SH; Y = H
b, X = Br(Cl); Y = H
c, X = OH; Y = H
d, X = SPh; Y = H
e, X = SCH_2Ph; Y = H
f, X = SPh; Y = CH_3
g, X = SCH_2Ph; Y = CH_3



IIa, X = Br; Y = H
b, X = OTs; Y = CH_3



III

By kinetic studies involving the S_N2 displacement of tosylate anion from methyl O-tosyl-(*S*)(+)-mandelate (IIb) by means of phenylmercaptide and benzylmercaptide nucleophiles, we have recently demonstrated[13] that the levorotatory enantiomers of α-phenylmercaptophenylacetic and α-benzylmercaptophenylacetic acids each possessed the (*R*) absolute configuration, Id and Ie, respectively. Similarly, optical rotatory dispersion measurements have since shown[14] that the levorotatory enantiomers of 2-phenyl-2-phenylmercaptopropanoic and 2-phenyl-2-benzylmercaptopropanoic acids likewise possessed the (*R*) configuration (If and Ig, respectively). It occurred to us that kinetic or rotatory dispersion studies analogous to these might shed light on the unknown absolute configuration of α-mercaptophe-

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nylacetic acid. In addition, configurational confirmation might be obtained and optical homogeneity might be estimated if a resolved sample of the latter acid could be converted under nonracemizing conditions into one of the configurationally established enantiomers of α-benzylmercaptophenylacetic acid (*e.g.*, Ie). Experiments along both of these lines are reported below.

At the outset we attempted to establish polarimetrically the presumed second-order displacement of OTs^- from methyl O-tosyl-(*S*)(+)-mandelate (IIb, 0.01 *M* in ethanol) by SH^- (0.01 *M* NaSH in ethanol), using techniques previously described.[13] The second-order rate constants calculated from the mutarotation data are given in the third column of Table I, where we see that the value of *k* is not constant, but increases approximately threefold during the course of the reaction. Such a monotonic increase in the second-order rate constant is explainable in terms of eq 1 to 3. Now, the rate constant values in Table I are calculated on the assumption of a single reaction product, methyl (−)-α-mercaptophenylacetate (IV), produced as in eq 1. However, the mercaptan IV in the presence of SH^- can provide the mercaptide ion V, as in eq 2, and the mercaptide ion V may in turn compete with SH^- for starting tosylate to form the sulfide by-product VI. Now, if the sulfide VI is *more levorotatory* than the initial products IV and V, its increasing formation as the reaction proceeds should lead to excessively rapid levo mutarotation, and an increasingly high calculated value for the second-order rate constant. This explanation predicts that in the presence of a large excess of SH,⁻ where reaction 1 can compete more effectively with 3, the value of *k* should show less of the above monotonic increase as the displacement progresses. This prediction is borne out in the 0.06 *M* NaSH experiment in Table I, where *k* increases only by a factor of 1.37 during the course of the reaction. Equation 2 also predicts the formation of H_2S during the reaction. In each experiment in Table I the formation of gas bubbles was noted in the polarimeter tube after the reaction had progressed for a time. Finally, the above explanation postulates a sulfide by-product (VI) which is more levorotatory than the desired mercaptan product (IV). This prediction was realized when the displacement was duplicated on a preparative scale. When methyl O-tosyl-(*S*)(+)-mandelate (1.5 g) was allowed to react with 5 equiv of sodium hydrosulfide in ethanol at room temperature during 1.5 hr, customary processing afforded 95% (based on IV) of crude product. This was separated by fractional distillation into two fractions, the first (68%) having $[\alpha]^{25}\mathrm{D}$ −54.2° (ethanol) and the second (32%; residue) having $[\alpha]^{25}\mathrm{D}$ −72.6° (ethanol). Elemental analyses for C, H, and S indicated that the first fraction consisted of 92.4% of the mercaptan IV and 7.6% of the sulfide VI, whereas the second fraction was 89.3% VI and 10.7% IV. From these data one may calculate that the chemically homogeneous methyl (−)-α-mercaptophenylacetate (IV) from this reaction would have $[\alpha]^{25}\mathrm{D}$ −52.5°, while the homogeneous α,α′-di(carbomethoxy)dibenzyl sulfide (VI) product would have $[\alpha]^{26}\mathrm{D}$ −75.0°. The optical homogeneities of these products are discussed below.

TABLE I

SECOND-ORDER RATE CONSTANTS FOR THE REACTION OF 0.01 *M* METHYL O-TOSYL-(*S*)(+)-MANDELATE WITH SODIUM HYDROSULFIDE

Time, min	0.01 *M* NaSH		0.06 *M* NaSH	
	α, deg[a]	*k*,[b] l. mol⁻¹ min⁻¹	α, deg[a]	*k*,[c] l. mol⁻¹ min⁻¹
2			0.29	1.37
4			0.19	1.40
6			0.09	1.52
8			0.02	1.52
10			−0.05	1.57
12			−0.11	1.65
15	0.30	1.20	−0.19	1.83
20			−0.26	1.88
30	0.18	1.43		
40	0.11	1.60		
52	0.04	1.84		
66	−0.02	2.00		
78	−0.06	2.09		
97	−0.12	2.40		
121	−0.18	2.77		
150	−0.23	3.40		

[a] In a 2-dm tube; $\alpha_0 = +0.41°$; $\alpha_\infty = -0.35°$. [b] Calculated by $(1/C - 1/C_0)/t$; $t_{1/2}$ = *ca.* 56 min. [c] Calculated by log $a(b - x)/b(a - x)$; $t_{1/2}$ = *ca.* 8 min.

$$(+)\text{-ROTs} + \text{SH}^- \longrightarrow \underset{\text{IV}}{(-)\text{-RSH}} + \text{OTs}^- \tag{1}$$

$$(-)\text{-RSH} + \text{SH}^- \rightleftharpoons \underset{\text{V}}{(-)\text{-RS}^-} + \text{H}_2\text{S} \tag{2}$$

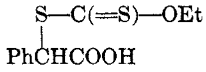
$$(+)\text{-ROTs} + (-)\text{-RS}^- \longrightarrow \underset{\text{VI}}{(-)\text{-RSR-}(-)} + \text{OTs}^- \tag{3}$$

$$\text{R} = \text{Ph}\overset{|}{\text{C}}\text{HCOOCH}_3$$

If the rate constants in Table I are extrapolated graphically back to zero time, the extrapolated value should provide a reasonable measure of the second-order rate constant for reaction 1, since under these conditions reaction 3 has not yet started to compete for available tosylate. Such an extrapolation provides an average value *k* = 1.18 l. mol⁻¹ min⁻¹ for the specific rate of displacement of tosylate ion from methyl O-tosyl-(*S*)-(+)-mandelate by hydrosulfide ion. This value is much lower than the previously measured[13] second-order rate constants for similar tosylate displacements involving benzylmercaptide and phenylmercaptide ions, 176 and 51 l. mol⁻¹ min⁻¹, respectively.

Although the "near-constancy" of the second-order rate constants in Table I, and the above experimentally confirmed rationalization for their monotonic increases argue strongly for an SN2 mechanism and Walden inversion in the conversion of the (*S*)(+)-tosylate IIb into methyl (−)-α-mercaptophenylacetate (IV), it was deemed desirable to confirm this conclusion independently under conditions which would permit a quantitative evaluation of the optical course of the displacement in question. The approach here was to attempt the resolution of (±)-α-mercaptophenylacetic acid [(±) Ia], then to establish both absolute configuration and optical purity by converting the resolved sample into its S-benzyl thio ether (*e.g.*, Ie) of known[13] absolute configuration.

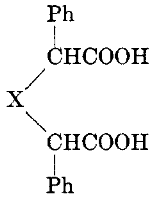
We initially attempted the preparation of methyl α-mercaptophenylacetate [(±) IV] by the action of sodium hydrosulfide on methyl α-chlorophenylacetate, obtained in turn by the action of PCl_5 on methyl mandelate. The crude ester product, however, was a complex mixture whose components were not readily separated, and hydrolysis was therefore not attempted. Attention was then given to the preparation of (±)-α-mercaptophenylacetic acid by hydrolysis of S-(thioncarboethoxy)-α-mercaptophenylacetic acid (VII), prepared



$$\begin{array}{l}\mathrm{S{-}C({=}S){-}OEt}\\ \quad|\\ \mathrm{PhCHCOOH}\end{array}$$

VII

in turn by the action of potassium O-ethyldithiocarbonate on α-chlorophenylacetic acid. Modifying earlier literature procedures (*cf.* Experimental Section), the desired (±)-α-mercaptophenylacetic acid, an oil in the crude state, was readily obtained in acceptable yield, and resolutions were then attempted with several optically active bases. These were unsuccessful with (−)-α-phenylethylamine and (+)-α-(1-naphthyl)ethylamine, but optical enrichment was finally achieved by systematic recrystallization of the cinchonidine salt. In the final recrystallization of the latter from 2:1 acetone–ethanol, a 31% material loss accompanied only a 2% increase in specific rotation, and resolution was therefore deemed essentially complete. That this was not the case, however, was shown by the facts that the crude (−)-α-mercaptophenylacetic acid recovered from the final cinchonidine salt had mp 76–83° and $[\alpha]^{25}\mathrm{D}$ −81.0° (ethanol), and that one recrystallization (1:3 benzene–hexane) raised these values to mp 87–87.5° and $[\alpha]^{25}\mathrm{D}$ −104.8° (ethanol). Another recrystallization gave a sample having mp 88–88.5° and $[\alpha]^{25}\mathrm{D}$ −106.2° (ethanol), −93.6° (ether), and optical homogeneity was again assumed to have been achieved. That this was still not the case, however, was shown by the S-benzylation studies described below. The recovery of residual α-mercaptophenylacetic acid from the original cinchonidine salt mother liquors of the above resolution afforded not only a weakly dextrorotatory {$[\alpha]^{25}\mathrm{D}$ +8.6° (ethanol)} sample of the acid, but also a 31% yield of dextrorotatory α,α′-dicarboxydibenzyl disulfide (VIII) {mp 217–218°, $[\alpha]^{25}\mathrm{D}$ +90.8° (acetone)} of



VIII, X = -S–S–
IX, X = -S–

unknown optical purity. The above (−)-α-mercaptophenylacetic acid readily formed a methyl ester having $[\alpha]^{25}\mathrm{D}$ −101.2° (ethanol).

S-Benzylation of the above (−)-α-mercaptophenylacetic acid was conducted in aqueous ethanol in the presence of 2 equiv of sodium bicarbonate and 1 equiv of benzyl bromide. The reaction, followed polarimetrically, was found to go to completion at 25° in less than 2 hr, and led to samples of (*R*)(−)-α-benzylmercaptophenylacetic acid (Ie) having $[\alpha]^{25}\mathrm{D}$ −129 ±3° (ethanol). Since the latter optically pure acid[13] has $[\alpha]^{25}\mathrm{D}$ −161°, the present sample was about 80.1% optically pure. The present acid on Fischer esterification afforded a methyl ester having $[\alpha]^{25}\mathrm{D}$ −116° (ethanol). Since optically pure methyl (*R*)(−)-α-benzylmercaptophenylacetate[13] has $[\alpha]^{25}\mathrm{D}$ −143°, the present ester is 80.6% optically pure, confirming the optical purity of its acid precursor. To estimate whether partial racemization might have attended the above S-benzylation reactions, the (−)-α-mercaptophenylacetic acid starting material, the (−)-α-benzylmercaptophenylacetic acid product, and a mixture of each were separately dissolved in sodium bicarbonate solution and observed polarimetrically at room temperature. Each solution proved optically stable well beyond the reaction times employed above, and it was therefore concluded that the S-benzylation reactions in question led to substantially unracemized products. If the (−)-α-mercaptophenylacetic acid employed above {$[\alpha]^{25}\mathrm{D}$ −106.2° (ethanol), −93.6° (ether)} was thus 80.3% (average) optically pure, the specific rotations of the optically homogeneous acid must accordingly be $[\alpha]^{25}\mathrm{D}$ −132.4° (ethanol) and −116.6° (ether). That of optically pure methyl (−)-α-mercaptophenylacetate (IV) must likewise be $[\alpha]^{25}\mathrm{D}$ −126.0° (ethanol).

The above conversion of (−)-α-mercaptophenylacetic acid into (*R*)(−)-α-benzylmercaptophenylacetic acid (Ie) shows unequivocally that the former acid likewise possesses the (*R*) absolute configuration (Ia), and that predominant inversion of configuration did in fact attend both the above transformation of methyl O-tosyl-(*S*)(+)-mandelate (IIb) into methyl (*R*)(−)-α-mercaptophenylacetate (IV), as well as Levene's conversion of (*R*)(−)-α-bromophenylacetic acid into (*S*)-(+)-α-mercaptophenylacetic acid. Levene's assumption of inversion in the latter reaction[1] was thus correct, although his configurational assignments were not.

Since the above preparative tosylate displacement led to a sample of methyl (*R*)(−)-α-mercaptophenylacetate which (if chemically homogeneous) has $[\alpha]^{25}\mathrm{D}$ −52.5°, we may conclude that this product was 41.7% optically pure (*i.e.*, 52.5/126). Similarly, the free acid obtained on hydrolysis of this ester sample had $[\alpha]^{25}\mathrm{D}$ −53.9° (ether), or was 46.2% optically pure (*i.e.*, 53.9/116.6), in reasonable agreement. The net optical course of our preparative conversion of methyl O-tosyl-(*S*)(+)-mandelate into methyl (*R*)(−)-α-mercaptophenylacetate was thus (average) about 44% inversion and 56% racemization. Subsequent polarimetric experiments (see Experimental Section) suggested that this racemization was probably inherent in the displacement reaction itself, and did not occur significantly after the product had formed. Our (−)-α,α′-di(carbomethoxy)dibenzyl sulfide (VI) by-product had $[\alpha]^{25}\mathrm{D}$ −75.0° (assuming chemical homogeneity). Janczewski, Pytlarz, and Poplawski[12] have recently resolved α,α-dicarboxydibenzyl sulfide (IX) and reported $[\alpha]^{25}\mathrm{D}$ −278° (MeOH) for the levorotatory enantiomer. If we assume that the same optical rotation ratio (1.05) exists between the latter acid and its methyl ester (VI) as exists between (−)-α-mercaptophenylacetic acid and its methyl ester, {*i.e.*, assume optically pure VI has $[\alpha]^{25}\mathrm{D}$ of about −264° (ethanol)}, it would appear that our sample of the by-product sulfide VI was about 28% optically pure.

From their reaction of (*R*)(−)-α-bromophenylacetic acid with potassium hydrosulfide, Levene and coworkers[1] report the isolation of a crude product having $[\alpha]^{20}\mathrm{D}$ +114.5° (ether). This they fractionally distilled. Half was collected at 148–152° (2 mm), had mp 80–87° and $[\alpha]^{20}\mathrm{D}$ +71.5° (ether), and was identified as (*S*)(+)-α-mercaptophenylacetic acid of 61% optical

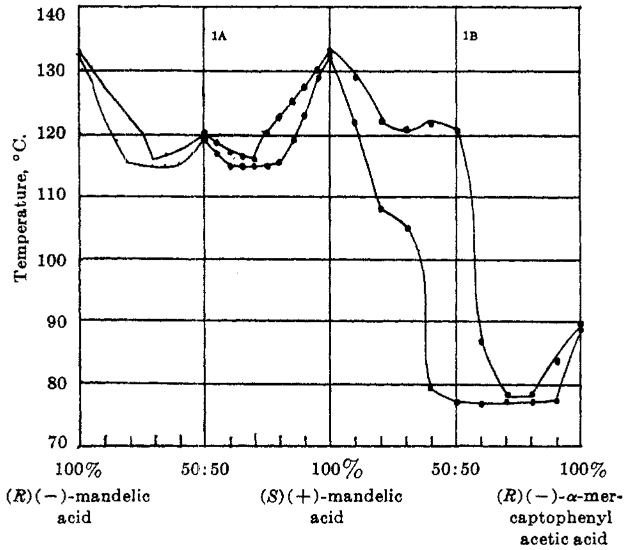


Figure 1.—Melting range–composition diagrams for mandelic and α-mercaptophenylacetic acids.

purity. The nonvolatile residue, mp 127–130°, $[\alpha]^{20}\text{D}$ +53.7° (ether), was assumed to be α,α′-dicarboxydibenzyl sulfide (IX). Commenting on the novelty of the above optical rotation results, Levene concluded that thermal racemization had attended the distillation of the (*S*)(+)-α-mercaptophenylacetic acid. We have attempted to substantiate this remarkable observation by heating a sample of our (*R*)(−)-α-mercaptophenylacetic acid at 150° for 15 min. Absolutely no racemization was noted, and we are at a loss to explain Levene's observation.

Finally, we have attempted to see if the above stereochemical conclusions could be confirmed by application of the method of quasi-racemates[15,16] to the antipodes of mandelic and α-mercaptophenylacetic acids. Whereas mixtures of (*S*)(+)- and (*R*)(−)-mandelic acids clearly show racemic compound formation in their melting range behavior (Figure 1A),[5,17] mixtures of either (*S*)(+)-mandelic or (*R*)(−)-mandelic acids with (*R*)(−)-α-mercaptophenylacetic acid showed melting point behavior characteristic only of solid solutions [Figure 1B; a practically identical curve was obtained with (*R*)(−)-mandelic acid], indicating again[14–16] that sulfur and oxygen analogs do not seem amenable to configurational comparisons by the quasi-racemate method.

Experimental Section

S-(Thioncarboethoxy)-α-mercaptophenylacetic Acid (VII).—Potassium hydroxide (20 g) was dissolved with magnetic stirring in 95% ethanol (100 ml). The solution was cooled to 0°, stirred rapidly, and treated all at once with carbon disulfide (35 ml; 1.63 equiv), resulting in precipitation of a yellow solid. This was slurried well with ether (200 ml), the mixture was filtered, and the cake was rinsed with ether. Additional solid precipitated in the filtrate; it was collected and rinsed with ether. The process was continued until no more solid precipitated. The crude potassium *o*-ethyldithiocarbonate (43.5 g, 76%) was dried in a vacuum desiccator and stored over P_2O_5 prior to use. The above procedure is a modification of that of Price and Stacy.[18]

The above product (26.5 g, 165.6 mmol) was dissolved in warm methanol (42 ml). The solution was cooled slightly and treated with a solution of α-chlorophenylacetic acid[19] (14.1 g, 82.7 mmol) in dioxane (83 ml), then was stoppered and stirred magnetically at room temperature for 23 hr, and was finally poured into ice water (500 ml). The mixture was extracted twice with ether (discard), then was acidified with dilute sulfuric acid and extracted thrice with ether. The extract was washed with water, dried ($MgSO_4$), and stripped of solvent to yield 21.5 g (101.6%) of crude product, a yellow oil which crystallized rapidly on seeding and scratching and which was hydrolyzed below without further purification.

In preliminary preparations the crude product was recrystallized from carbon tetrachloride with considerable material loss, mp 90.5–91.5°. A second recrystallization gave a sample, mp 91–91.5°, whose infrared spectrum in chloroform was identical in all respects with that of the crude product above, with the exception of the presence of two small bands at 11.23 and 11.43 μ, respectively, in the spectrum of the crude sample. Iskander and Tewfik report[11] mp 95–96° for this product.

Anal. Calcd for $C_{11}H_{12}O_3S_2$: C, 51.54; H, 4.72; S, 25.02. Found: C, 51.43; H, 4.81; S, 25.24.

α-Mercaptophenylacetic Acid [(±) Ia].—The above crude acid (21.5 g) was dissolved in ethanol (78 ml) and treated with concentrated ammonium hydroxide (50 ml). The flask was flushed with illuminating gas, stoppered, and allowed to stand at room temperature for 72 hr, whereupon the flask contents were stripped of solvent by rotary vacuum evaporation at 100°. The residue was dissolved in dilute ammonium hydroxide (1:1, 100 ml) and extracted twice with ether (discard). The ammoniacal layer was acidified with iced 30% sulfuric acid and extracted twice with ether. The extract was washed with water, dried ($MgSO_4$), and freed of ether to yield 13.85 g (98%) of thin, vile-smelling oil.

In a parallel experiment starting with 11.1 g of recrystallized acid VII, mp 83.5–86.5°, 7.4 g (101%) of similar crude, oily product was obtained, $n^{24}\text{D}$ 1.5665, whose infrared spectrum was identical with that of the above product and whose analysis bordered on acceptability.

Anal. Calcd for $C_8H_8O_2S$: C, 57.12; H, 4.79. Found: C, 56.34; H, 5.32.

A preliminary attempt to hydrolyze the acid VII by heating at 100° for 20 hr in a mixture of acetic acid–water–sulfuric acid (9:5:1) was ineffective, and only starting acid was recovered, as indicated by infrared spectra and crystallinity. The above ammonolysis is an adaptation of the procedure of Biilmann.[20]

Methyl α-Mercaptophenylacetate.—A mixture of the above α-mercapto acid (1.00 g) in methanol (15 ml) containing sulfuric acid (0.5 ml) was heated under reflux for 6 hr, cooled, and poured into water. Ether extraction, followed by customary washing, drying, and solvent removal, afforded 0.98 g (90.7%) of crude ester, a thin, colorless oil. The product was kept overnight over P_2O_5 at 0.1 mm, whereupon it showed $n^{25}\text{D}$ 1.5480 and proved homogeneous on thin layer chromatography (silica gel G, benzene eluent).

Anal. Calcd for $C_9H_{10}O_2S$: C, 59.32; H, 5.53; S, 17.59. Found: C, 59.84; H, 5.46; S, 17.25.

α,α′-Dicarboxydibenzyl Disulfide (VIII).—The above α-mercapto acid (0.70 g) was dissolved in acetic acid (4 ml) and treated with 30% hydrogen peroxide (0.25 g, 5% excess) in acetic acid (3 ml). After 2.5 hr at room temperature the mixture was poured into water, then extracted twice with ether. Usual processing yielded 0.70 g of white solid, which was slurried with a mixture of benzene (2 ml) and hexane (4 ml), then filtered. The residue, 0.3 g, mp 210–214°, was recrystallized from a mixture of acetone (2 ml), benzene (4 ml), and hexane (10 ml) to provide 0.11 g of product having mp 215.5–216°, in agreement with the value (218°) reported by Iskander and Tewfik.[11]

S-Benzylation of α-Mercaptophenylacetic Acid.—The above α-mercapto acid (0.70 g; 4.16 mmol) was dissolved in ethanol (8.3 ml) and treated with benzyl bromide (0.492 ml, 4.16 mmol). The mixture was treated with a solution of sodium bicarbonate (0.70 g, 8.33 mmol) in water (4.2 ml), then was heated under reflux for 25 min, cooled, poured into water, and acidified with dilute sulfuric acid. Ether extraction and customary work-up afforded 1.00 g (93.5%) of a thick oil which quickly solidified

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and whose infrared spectrum was identical with that of authentic α-benzylmercaptophenylacetic acid. The product was dissolved in benzene (2.5 ml) and filtered from a small amount (0.02 g) of insoluble product, mp 216–216.5°. The filtrate was treated with hexane to incipient turbidity, seeded, and chilled, yielding 0.10 g of product having mp 84.5–85.5°, which gave no mixture melting point depression with authentic α-benzylmercaptophenylacetic acid (mp 86°). The above insoluble product gave no mixture melting point depression with the above sample of the disulfide (VIII) from α-mercaptophenylacetic acid, indicating that a small amount of air oxidation competed with S-benzylation under the present conditions.

Resolution of α-Mercaptophenylacetic Acid.—The above racemic α-mercapto acid (13.35 g) was dissolved in acetone, as was 23.30 g of cinchonidine. The solutions were mixed and diluted to 150 ml with acetone, seeded with material from a small-scale resolution, and allowed to stand 2 hr. The salt obtained (a), 11.38 g, had mp 162.5° and $[\alpha]^{25}\text{D}$ −91.0° (*c* 1.3, 95% ethanol). Only a small amount of additional material (0.22 g, mp 158–161°) resulted on placing the mother liquors at 0° overnight. The mother liquors were accordingly evaporated to dryness and the residue was redissolved in 45 ml acetone, seeded, and chilled. This produced 5.10 g of additional salt (b): mp 147–153° (softening from 70°); $[\alpha]^{25}\text{D}$ −81.7° (*c* 1.0, 95% ethanol). The first product (a) was recrystallized at 0° from a mixture of ethanol (25 ml) and acetone (150 ml) to yield 4.64 g of solid (c): mp 164–165.5°; $[\alpha]^{25}\text{D}$ −99.6° (*c* 0.7; 95% ethanol). Product b was recrystallized from acetone (25 ml) to produce 2.40 g of d: mp 154.5–156.5°; $[\alpha]^{25}\text{D}$ −92.9° (*c* 0.7, 95% ethanol). The mother liquors from c were evaporated to dryness, the residue was combined with d, and the mixture was recrystallized from ethanol (6 ml) and acetone (50 ml), affording 5.04 g of e: mp 159.5–162°; $[\alpha]^{25}\text{D}$ −90.0° (*c* 1.5, 95% ethanol). The latter was again recrystallized from ethanol (4 ml) and acetone (25 ml) to give 2.33 g of f: mp 168°; $[\alpha]^{25}\text{D}$ −98.1° (*c* 1.0, 95% ethanol). Crops c and f were combined and recrystallized from ethanol (8 ml) and acetone (15 ml) to obtain 4.80 g of g: mp 171°; $[\alpha]^{25}\text{D}$ −101° (*c* 0.7, 95% ethanol). In view of the little change in rotation during the last recrystallization, it was (erroneously) concluded that the final cinchonidine salt (g) was practially optically pure.

Anal. Calcd for $C_{27}H_{30}N_2O_3S$: C, 70.11; H, 6.54; N, 6.06; S, 6.92. Found: C, 70.25; H, 6.64; N, 6.10; S, 6.91.

The salt g (4.4 g) was dissolved in a little warm ethanol and the solution was added to an excess of 10% sulfuric acid. The mixture was extracted thrice with ether, and the extract was washed with water, dried, and stripped of solvent. There resulted 1.64 g (102%) of thin syrup which soon crystallized as long needles: mp 76–83°; $[\alpha]^{25}\text{D}$ −81.0° (*c* 1.3, 95% ethanol). These were recrystallized from a mixture of benzene (2 ml) and hexane (6 ml) to produce 1.00 g of product having mp 87–87.5° and $[\alpha]^{25}\text{D}$ −104.8° (*c* 0.5, 95% ethanol). Another recrystallization from benzene (1.3 ml) and hexane (5 ml) gave 0.90 g of (−)-α-mercaptophenylacetic acid having mp 88–88.5 and $[\alpha]^{25}\text{D}$ −106.2° (*c* 0.5, 95% ethanol), −93.6° (*c* 0.9, ether).

Anal. Calcd for $C_8H_8O_2S$: C, 57.12; H, 4.79; S, 19.06. Found: C, 57.46; H, 4.86; S, 19.17.

While the above results indicate that the original cinchonidine salt (g) was not optically pure, the reasonably similar melting point and rotation before and after the final recrystallization of the recovered acid led us, again erroneously, to assume that optical purity had been substantially achieved. The infrared spectrum ($CHCl_3$ solution) of the final (−)-α-mercaptophenylacetic acid and its racemic oily precursor were identical in all respects. The structure of the resolved acid was confirmed by its integrated nmr spectrum ($CDCl_3$, tetramethylsilane internal standard, Varian A60 nmr spectrometer). The single thiol proton appeared as a doublet centered at δ 2.60 (J = 8 Hz); the lone α proton appeared as a doublet centered at 4.68 (J = 8 Hz); the five aromatic protons appeared as a complex multiplet centered around 7.37; and the single carboxyl proton appeared as a singlet at 11.47.

The original cinchonidine salt mother liquors from the above resolution were evaporated to dryness and the residue (19.95 g) was decomposed with dilute sulfuric acid as above. Similar processing yielded 6.72 g (92.6%) of a semisolid paste. This was slurried with benzene and filtered. The insoluble residue (2.03 g) had mp 217–218° and $[\alpha]^{25}\text{D}$ 90.8° (*c* 1.2; acetone). The residue from evaporation of the filtrate was 4.51 g of amber oil which gradually crystallized, $[\alpha]^{25}\text{D}$ +8.6° (*c* 4.4; 95% ethanol). The insoluble residue proved to be the dextrorotatory form of the disulfide VIII, of unknown optical purity. Its recrystallization from acetone–benzene did not lead to optical enrichment but yielded 0.59 g: mp 220–221° dec; $[\alpha]^{25}\text{D}$ +75.3° (*c* 0.76, acetone).

Anal. Calcd for $C_{16}H_{14}O_4S_2$: C, 57.46; H, 4.22; S, 19.18. Found: C, 57.67; H, 4.34; S, 19.15.

The decomposition with acid of several other intermediate fractions of cinchonidine salts from the above resolution similarly led to residues from which high melting (209–215°) optically active products, presumably also optically impure analogous disulfides, were isolated.

At the outset, resolution of the above racemic α-mercaptophenylacetic acid was attempted with both α-phenylethylamine and with (+)-α-(1-naphthyl)ethylamine. In each case crystalline salts were readily obtained, but their recrystallization led to little apparent optical enrichment. Acid decomposition of the thrice recrystallized salt from the latter amine gave an optically inactive sample of recovered acid which again contained about 10% of the disulfide VIII.

Methyl (−)-α-Mercaptophenylacetate.—The above (−)-α-mercaptophenylacetic acid (0.150 g) was heated for 7 hr in methanol (5 ml) containing sulfuric acid (0.2 ml). Processing as before yielded 0.143 g (88%) of colorless oil, $[\alpha]^{25}\text{D}$ −101.2° (*c* 1.4; 95% ethanol), which was homogeneous on thin layer chromatography (silica gel G; benzene) and showed the same R_f value as the racemic sample above.

Anal. Calcd for $C_9H_{10}O_2S$: C, 59.32; H, 5.53; S, 17.59. Found: C, 59.95; H, 5.63; S, 17.71.

S-Benzylation of (−)-α-Mercaptophenylacetic Acid.—The reaction was conducted under polarimetric observation at room temperature, in order to employ the gentlest convenient conditions. The above (−)-α-mercaptophenylacetic acid (120 mg, 0.714 mmol) and sodium bicarbonate (120 mg, 1.428 mmol) were dissolved in water (5 ml). Benzyl bromide (124 mg, 0.725 mmol) was dissolved in 95% ethanol (6 ml) and the two solutions were mixed and placed in a 1-dm polarimeter tube. The following rotations were observed at the following times (min): −1.38° (4.5), −1.47° (7), −1.62° (10), −1.85° (22), −2.09° (42), −2.22° (50), −2.38° (80), −2.50° (125), −2.50° (185), −2.45° (1260). The reaction mixture was poured into water, acidified with dilute sulfuric acid, and extracted twice with ether. Washing, drying, and solvent removal left 135 mg (73.4%) of turbid oil having $[\alpha]^{25}\text{D}$ −126° (*c* 1.6, 95% ethanol), which showed an infrared spectrum (0.138 M solution, $CHCl_3$) identical in all respects with the spectrum (0.138 M solution, $CHCl_3$) of authentic (−)-α-benzylmercaptophenylacetic acid, $[\alpha]^{25}\text{D}$ −161° (ethanol). The crude oil was dried over P_2O_5 at 0.1 mm for 12 hr prior to analysis.

Anal. Calcd for $C_{15}H_{14}O_2S$: C, 69.74; H, 5.46; S, 12.41. Found: C, 68.81; H, 5.45; S, 12.64.

The above mutarotation data were subjected to second-order rate constant calculations as previously described.[13] The data afforded a reasonably constant value k = 0.72 ± 0.05 l. mol^{-1} min^{-1} during the first 70% of the reaction, after which the rate constant appeared to increase. The reaction half-life was about 22 min under the conditions noted.

In confirmation of the above experiment (−)-α-mercaptophenylacetic acid (120 mg) and sodium bicarbonate (120 mg, 2 equiv) in water (6 ml) were mixed with benzyl bromide (360 mg, 3 equiv) in ethanol (8 ml). After 150 min the product was isolated as before, a clear oil which slowly crystallized, $[\alpha^{25}\text{D}]$ −132° (*c* 1.2, 95% ethanol).

In order to estimate whether partial racemization might have attended the above S-benzylation reactions, the starting material, the product, and a mixture of each were examined polarimetrically in bicarbonate solution. (−)-α-Mercaptophenylacetic acid (0.214 mmol) and sodium bicarbonate (0.428 mmol) in water (3.0 ml) showed a rotation of −1.38°/dm, unchanged during 26 hr. (−)-α-Benzylmercaptophenylacetic acid (0.713 mmol) and sodium bicarbonate (1.428 mmol) in water (10 ml) had a rotation of −3.37°/dm, unchanged after 120 hr. A solution of (−)-α-mercaptophenylacetic acid (0.214 mmol), (−)-α-benzylmercaptophenylacetic acid (0.214 mmol), and sodium bicarbonate (0.918 mmol) in 50% ethanol (10 ml) had a rotation of −1.61°/dm, unchanged in 3 hr. It thus seems probable that the above S-benzylation reactions were attended by no significant racemization of starting material or product during the time periods and under the conditions employed.

Methyl (−)-α-Benzylmercaptophenylacetate.—A mixture of the combined (−)-α-benzylmercaptophenylacetic acid described above (62.5 mg), methanol (3 ml), and sulfuric acid (0.15 ml) was heated under reflux for 6 hr, cooled, and poured into water. Ether extraction and customary processing afforded 54 mg (82%) of crude ester, an oil having $[\alpha]^{25}\text{D}$ −116° (*c* 1.3, 95% ethanol). This had an infrared spectrum (in 0.14 *M* $CHCl_3$ solution) identical in all respects with that of authentic methyl (−)-α-benzylmercaptophenylacetate at the same concentration. The two samples showed identical R_f values on thin layer chromatography. Since the optically pure ester had $[\alpha]^{25}\text{D}$ −143°, the present sample thus appeared to be 80.6% optically pure.

Displacement Rates of Methyl O-Tosyl-(*S*)(+)-mandelate with Sodium Hydrosulfide.—A 0.01 *M* solution of 32.0 mg of tosylate IIb in absolute ethanol (10 ml) saturated with H_2S showed an optical rotation of 0.41°/2 dm. This value was used below as α_0. A solution of the tosylate (32.0 mg) in ethanol (4.5 ml) was saturated with H_2S, then adjusted to 5.0 ml. A solution of sodium ethylate (0.115 ml, 0.02 g of Na/ml of ethanol) was diluted to 4.5 ml with absolute ethanol, saturated with H_2S, and adjusted to 5.0 ml. At t_0 the two solutions were mixed (providing a solution 0.01 *M* in tosylate and 0.01 *M* in NaSH) and placed in a 2-dm all-glass polarimeter tube at room temperature (21°). The tube side arm was stoppered after flushing with H_2S and the solution was observed polarimetrically at various time intervals, with the results shown in the first two columns of Table I. The data in the first and fourth column of Table I were obtained in the same way except that the NaSH solution was prepared using 0.69 ml of the above sodium ethylate solution, thus providing that the final NaSH concentration be 0.06 *M*. In each experiment a few small bubbles of H_2S were evolved during the course of the reaction, and the equilibrium rotation was −0.35°/2 dm.

From a straight-line plot of percentage composition *vs.* optical rotation (100% tosylate, α_0 +0.41°; 100% product, α_∞ −0.35°) the concentration of remaining tosylate was estimated for each time value in Table I, as previously described.[13] These concentration and time values were used in standard equations[21] to calculate the second-order rate constant applying at each data point. The rate constants so calculated for each experiment are summarized in Table I. The final α_∞ values (−0.35°) in the above experiments corresponded to a methyl (−)-α-mercaptophenylacetate (IV) product which was *ca.* 20% racemized (see below).

Racemization of Methyl (−)-α-Mercaptophenylacetate by Sodium Hydrosulfide.—To test how extensively the products in the above rate experiments might themselves have been racemized by the reaction environment, the following experiment was performed. The above methyl (−)-α-mercaptophenylacetate ($[\alpha]^{25}\text{D}$ −101.2°, 80.3% optically pure, 18.2 mg, 0.1 mmol) was dissolved in absolute ethanol (5.0 ml) and the solution was saturated with H_2S. A solution of sodium ethylate (0.46 ml, 0.02 g of Na/ml of ethanol, 0.4 mmol) was diluted to 4.5 ml with absolute ethanol, saturated with hydrogen sulfide, and diluted to 5.0 ml. The two solutions were mixed (providing a solution 0.01 *M* in ester and 0.04 *M* in NaSH), placed in a 2-dm polarimeter tube, and observed as follows (*t*, min; α, deg/2 dm): 5, −0.36°; 30, −0.35°; 90, −0.35°; 150, −0.34°; 300, −0.28°; 1440, −0.04. Thus racemization of product does occur, but apparently not at a rate rapid enough to be significant during the reaction times involved in the rate experiments above. The fact that the starting rotation in the present experiment (0.01 *M* in methyl ester IV) was identical with the final rotation in the above rate experiments (also approximately 0.01 *M* in methyl ester) suggests that the ester products in the latter experiments were also about 80% optically pure.

Preparative Displacement of Methyl O-Tosyl-(*S*)(+)-mandelate with Sodium Hydrosulfide.—The present experiment was designed on the basis of reaction conditions in the above rate studies. A solution of the tosylate (1.50 g) in absolute ethanol (25 ml) was saturated with hydrogen sulfide, as was a solution of sodium (0.54 g, 5 equiv) in absolute ethanol (25 ml). The two solutions were mixed (providing a solution 0.0938 *M* in tosylate and 0.47 *M* in NaSH), the air above the solutions was displaced with hydrogen sulfide, and the flask was stoppered and allowed to stand at room temperature. After 1 min the solution precipitated sodium tosylate, and after 1.5 hr it was poured into water (300 ml) containing acetic acid (5 ml) and sodium chloride. The mixture was extracted three times with ether and the extract was washed with water, dried ($MgSO_4$), and freed of solvent to yield 814 mg (95.4% based on methyl α-mercaptophenylacetate) of vile-smelling, mobile oil. The crude product was distilled in a microstill at 0.1 mm with bath temperatures 130–150°. The thin, clear distillate weighed 366 mg and had $[\alpha]^{25}\text{D}$ −54.2° (*c* 2.5, 95% ethanol). Its analysis showed it to be methyl (−)-α-mercaptophenylacetate (IV) contaminated with (−)-α,α-'di-(carbomethoxy)dibenzyl sulfide (VI).

Anal. Calcd for $C_9H_{10}O_2S$: C, 59.32; H, 5.53; S, 17.59. Found: C, 59.85; H, 5.61; S, 17.07.

Assuming the sulfide VI to be the only contaminant, the above analysis indicates the product to be (average) 92.4% the methyl ester IV and 7.6% the sulfide VI.

The undistilled residue from the above distillation was washed from the still pot with ether. The solvent was removed to yield 174 mg of thick syrup, $[\alpha]^{25}\text{D}$ −72.6° (*c* 1.4, 95% ethanol). Its analysis indicated a mixture containing (average) 89.3% the sulfide VI and 10.7% methyl (−)-α-mercaptophenylacetate (IV).

Anal. Calcd for $C_{18}H_{18}O_4S$: C, 65.43; H, 5.49; S, 9.70. Found: C, 64.67; H, 5.36; S, 10.42.

The above-deduced compositions of the distillate and residue after distillation of the crude product permit us to calculate that, if chemically homogeneous, the above methyl (−)-α-mercaptophenylacetate (IV) would have $[\alpha]^{25}\text{D}$ −52.5° (95% ethanol) and the above (−)-sulfide VI would have $[\alpha]^{25}\text{D}$ −75.0° (95% ethanol). The methyl (−)-α-mercaptophenylacetate product was thus only 41.7% optically pure.

Hydrolysis of Methyl (−)-α-Mercaptophenylacetate.—The above methyl (−)-α-mercaptophenylacetate distillate {$[\alpha]^{25}\text{D}$ −54.2° (95% ethanol); 145.4 mg} was dissolved in a mixture of ethanol (1 ml) and *t*-butyl alcohol (4 ml). Water (8 ml) and sulfuric acid (0.5 ml) were added and the mixture was heated under reflux for 8 hr, then poured into 50 ml of water, cooled, and made alkaline with 5% potassium hydroxide solution. The solution was extracted twice with ether (discard), acidified with dilute sulfuric acid, and reextracted twice with ether. The extract was processed as usual to yield 117.5 mg (87.5%) of crude (−)-α-mercaptophenylacetic acid, a colorless, thick oil which crystallized on standing, $[\alpha]^{25}\text{D}$ −53.9° (*c* 1.8, ether). Since optically pure (−)-α-mercaptophenylacetic acid should have[13] $[\alpha]^{25}\text{D}$ −116.6° (ether), the above product appears about 46.2% optically pure, in reasonable agreement with the optical purity of its methyl ester precursor.

Attempted Thermal Racemization of (−)-α-Mercaptophenylacetic Acid.—To test the report of Levene and coworkers[1] that α-mercaptophenylacetic acid racemizes during distillation at 148–152° (1.8 mm), the above (−)-α-mercaptophenylacetic acid {$[\alpha]^{25}\text{D}$ −93.6° (ether); 29.0 mg} was placed in a small test tube and heated to 145–150° for a period of 15 min in a stirred heating bath. After cooling, the solidified melt (29.0 mg) showed $[\alpha]^{25}\text{D}$ −94.1° (*c* 0.97, ether), indicating that thermal racemization had not occurred under the conditions employed.

Quasi-Racemate Studies.—The melting point–composition diagrams in Figure 1 were obtained using the enantiomers of mandelic acid (A) and the above (*R*)(−)-α-mercaptophenylacetic acid, along with both (*S*)(+)- (B) and (*R*)(−)-mandelic acids. The techniques of preparing the mixture of different compositions, and of determining the melting range of these mixtures, were exactly as previously described.[14]

Registry No.—(±) Ia, 16201-50-6; (−) Ia, 16201-51-7; Ie, 13136-52-2; IIb, 13136-53-3; IV, 16201-52-8; VIII, 16201-54-0; methyl α-mercaptophenylacetate, 14337-72-5.

Acknowledgment.—We are indebted to the National Institutes of Health (GM-06232-08) for its generous support of a portion of this research during the summer of 1967.

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