The Absolute Configurations of Some α-Thio Ethers Derived from Atrolactic Acid[1]

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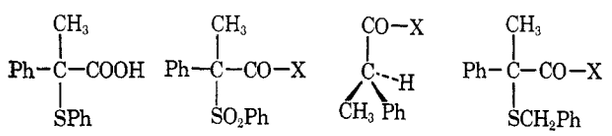
For accurate evaluation of the stereochemical course of the Raney nickel desulfuration of the optically active sulfone IIa and related analogs, it became necessary to establish unambiguously the absolute configurations of the enantiomers of 2-phenyl-2-phenylmercapto- (I) and 2-phenyl-2-benzylmercaptopropanoic acids (IVa). The preparation and resolution of these acids are described, as is their conversion to crystalline amide enantiomers. For reference purposes, O-benzyl-(*S*)-(−)- and O-benzyl-(*R*)-(+)-atrolactamides (VIb) have been prepared from (*S*)-(+)- and (*R*)-(−)-atrolactic acid precursors. The preparation involved conversion of the methyl esters of the latter to their sodium salts using sodium hydride, reaction of these salts with benzyl bromide, hydrolysis of the O-benzylated esters, and conversion of the resulting acids to crystalline amides, the enantiomers of VIb. Attempts were made to relate the known configurations of the latter amides with the enantiomeric amides IVb by seeking evidence for quasi-racemate formation in their mixture melting point diagrams. The method failed, however, in that mixtures of (+)-IVb and either enantiomer of VIb formed only solid solutions, and neither formed a quasi-racemate. Correlation was finally achieved through optical rotatory dispersion measurements on the N,N-diethylaminothiocarbamide derivatives of enantiomers of the acids I, IVa, and VIa. The derivatives from all levorotatory acids showed negative Cotton effects, while those from dextrorotatory acids showed positive Cotton effects. These data indicate that (−)-I and (−)-IVa possess the *R* configuration of (−)-VIe. O-Benzyl-(*S*)-(−)-atrolactamide suffered Raney nickel hydrogenolysis to (*R*)-(−)-hydratropamide with retention of configuration and with 84% preservation of optical purity.

Some 15 years ago, in initiating studies on the stereochemical course of reductive desulfuration, we prepared[2] the enantiomers of 2-phenyl-2-phenylmercaptopropanoic acid, (+)- and (−)-I, and from each of these the corresponding enantiomers of the sulfone analog, 2-phenyl-2-benzenesulfonylpropanoamide, (+)- and (−)-IIa. When (−)-IIa was desulfurated with Raney



I IIa, X = NH_2; b, X = OEt IIIa, X = NH_2; b, X = OEt; c, X = OH IVa, X = OH; b, X = NH_2; c, X = OEt

nickel in refluxing ethanol, (*R*)-(−)-hydratropamide, IIIa,[3] was formed in over 50% optical homogeneity.[2] Similarly, when the analogous levorotatory sulfone ester (−)-IIb was desulfurated with Raney nickel, ethyl (*R*)-(−)-hydratropate, IIIb, of high optical purity was likewise produced.[2] Freudenberg's "rules of rotational shifts"[4] were then applied[2] to two very limited series of derivatives (acid, acid chloride, ethyl ester, amide) related to (−)-I and (*R*)-(−)-hydratropic acid, IIIc. On the basis of the opposing optical rotation trends observed in the two series, it was provisionally suggested that (−)-I and (−)-IIIc had opposite configurations and that Walden inversion had attended the reductive desulfurations in question. A tentative mechanism rationalizing this hypothesis was proposed.[2] Recently a series of unexpected observations (to be reported subsequently) pertaining to the optical course of the desulfuration of sulfone IIa and compounds similar to it has led us to the need of establishing unambiguously the absolute configurations of the enantiomers of I, as well as those of 2-phenyl-2-benzylmercaptopropanoic acid, IVa. The present paper describes these configurational studies.

(−)-Mandelic acid and (−)-atrolactic acid are each known to have the absolute *R* configurations Va and VIa, respectively, on the basis of both optical rotation trends,[5] stereoselective syntheses,[6,7] and direct chemical

Va, X = OH; Y = H; b, X = OH; Y = CH_2Ph VIa, X = OH; Y = H; b, X = NH_2; Y = CH_2Ph; c, X = OEt, Y = CH_2Ph; d, X = OMe; Y = CH_2Ph; e, X = OH; Y = CH_2Ph

interconversions.[8-10] At the outset we chose to attempt an application of Fredga's quasi-racemate method[11] to the enantiomeric amides of the benzyl ethers of type VIb which, obtained herein for the first time from the enantiomers of VIa, are of known configuration, and to the benzyl thio ether amides of type IVb of unknown configuration. Mislow has confirmed[12] the configuration of hydratropic acid (IIIc) by this method, but found it inapplicable to the configurational correlation of mandelic (Va) and atrolactic acids (VIa).

Racemic 2-phenyl-2-benzylmercaptopropanoic acid (IVa) was conveniently synthesized by the reaction sequence: ethyl 2-chloro-2-phenylpropanoate[2] ($PhCH_2$-SNa) → ethyl 2-phenyl-2-benzylmercaptopropanoate (10% NaOH, 50°, 2.5 days) → IVa, mp 113–114°. The nmr spectrum of IVa (see Experimental Section) accorded with its indicated structure. Resolution of

(1) This constitutes communication XVI in the series, "The Stereochemistry of Raney Nickel Action." For XV, see W. A. Bonner and R. A. Grimm, *J. Org. Chem.*, **31**, 4304 (1966); for XIV, see W. A. Bonner, *J. Am. Chem. Soc.*, **82**, 1382 (1960).

(2) W. A. Bonner, *ibid.*, **74**, 1034 (1952).

(3) (a) E. L. Eliel, "Stereochemistry of Carbon Compounds," McGraw-Hill Book Co., Inc., New York, N. Y., 1962, pp 89, 93; (b) E. L. Eliel and J. P. Freeman, *J. Am. Chem. Soc.*, **74**, 923 (1952).

(4) K. Freudenberg, "Stereochemie," F. Deuticke, Leipzig and Vienna, 1933, p 695 ff.

(5) K. Freudenberg, J. Todd, and R. Seidler, *Ann.*, **501**, 199 (1933).

(6) V. Prelog, *Helv. Chim. Acta*, **36**, 308 (1953).

(7) V. Prelog and H. L. Meier, *ibid.*, **36**, 320 (1953).

(8) K. Mislow, *J. Am. Chem. Soc.*, **73**, 3954 (1951).

(9) J. H. Brewster, *ibid.*, **78**, 4061 (1956).

(10) D. J. Cram, K. R. Kopecky, F. Hauck, and A. Langemann, *ibid.*, **81**, 5754 (1959).

(11) (a) A. Fredga in "The Svedberg," Almqvist and Wiksells, Upsala, 1944, p 261 ff; (b) *Tetrahedron*, **8**, 126 (1960).

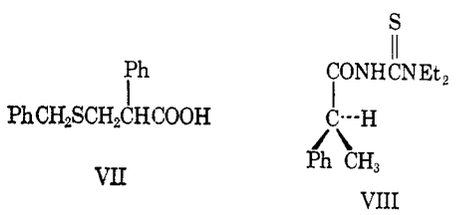
(12) K. Mislow and M. Heffler, *J. Am. Chem. Soc.*, **74**, 3668 (1952).

TABLE I

PHYSICAL PROPERTIES OF BENZYLOXY AND BENZYLMERCAPTO DERIVATIVES RELATED TO ATROLACTIC ACID

	Mp, °C	$[\alpha]^{24-28}D$, deg	Concn, g/100 ml	Solvent
O-Benzyl-(±)-atrolactic acid	93.5			
O-Benzyl-(*S*)-(+)-atrolactic acid	Oil	4.1	12.2	EtOH
O-Benzyl-(*R*)-(−)-atrolactic acid (VIe)	Oil	−3.7	11.5	EtOH
O-Benzyl-(±)-atrolactamide	112.5–113			
O-Benzyl-(*S*)-(−)-atrolactamide	141.5–142	−13.8	1.2	Me_2CO
O-Benzyl-(*R*)-(+)-atrolactamide (VIb)	141.5–142	13.1	1.1	Me_2CO
(±)-2-Phenyl-2-benzylmercaptopropanoic acid (IVa)	113–114			
(*S*)-(+)-2-Phenyl-2-benzylmercaptopropanoic acid ((+)-IVa)	Oil	46.6	2.3	EtOH
(*R*)-(−)-2-Phenyl-2-benzylmercaptopropanoic acid ((−)-IVa)	Oil	−46.5	2.2	EtOH
(*S*)-(+)-2-Phenyl-2-benzylmercaptopropanoamide ((+)-IVb)	107.5–108	14.5	0.7	EtOH
(*R*)-(−)-2-Phenyl-2-benzylmercaptopropanoamide ((−)-IVb)	107.5–108	−14.1	1.1	EtOH

IVa was accomplished as previously described[2] for the phenyl analog I, using sequentially the enantiomers of α-phenylethylamine. The resolved antipodes of IVa were converted into the enantiomeric amides (+)- and (−)-IVb by the usual action of thionyl chloride, followed by ammonium hydroxide.[2] When the above ester hydrolysis with 10% sodium hydroxide solution was conducted at 100° (6 hr) rather than 50° (2.5 days), two hydrolysis products were noted, the above desired racemic IVa as well as a second acid whose elemental analysis and nmr spectrum showed it to be the isomeric 2-phenyl-3-benzylmercaptopropanoic acid, VII. Formation of the latter product can be rationalized on the basis of an E2 elimination reaction on IVa to produce benzyl mercaptan and atropic acid, followed by anti-Markovnikov readdition[13] of the mercaptan to the atropic acid under our isolation conditions (*cf.* Experimental Section).



The preparation of the enantiomers of O-benzylatrolactamide, (+)- and (−)-VIb, presented unexpected complications. The synthesis of levorotatory ethyl O-benzyl-(*S*)-(−)-atrolactate, the enantiomer of VIc, $[\alpha]D$ −10.96° (EtOH), bp 152–153° (1 mm), has been claimed by Imaizumi[14] to result on heating for 6 hr benzyl chloride (4.6 g) and a solution of the sodium salt of ethyl (*S*)-(+)-atrolactate, prepared in turn by heating a solution of sodium (0.9 g) in *t*-butyl alcohol (30 ml) with ethyl (*S*)-(+)-atrolactate (8 g) for 2 hr. We attempted the similar preparation of racemic methyl ester VId but obtained incomplete O-benzylation, even on extending the reaction time. Hydrolysis of the crude ester product yielded only a solid whose infrared spectrum was identical with that of atrolactic acid. In retrospect it was obvious that the above reaction conditions could never result in complete conversion of atrolactates into benzylated esters such as VIc and VId, and that an alternative synthesis must be devised. Methyl atrolactate, therefore, was converted to its sodium salt by the action of sodium hydride suspended in butyl ether whereby close to the theoretical volume of hydrogen was liberated. The sodium salt was heated with excess benzyl bromide, and the resulting crude ester, racemic VId, was hydrolyzed with refluxing 10% aqueous potassium hydroxide. Customary processing afforded racemic O-benzylatrolactic acid, (±)-VIe, in 95% yield, mp 93.5°, whose nmr spectrum (*cf.* Experimental Section) accorded with the indicated structure. The enantiomers of this acid were then prepared in the same way starting, respectively, with methyl (*S*)-(+)- and (*R*)-(−)-atrolactates. They proved to be thick syrups with specific rotations approximately ±4° (Table I). Conversion of these syrupy enantiomers *via* acid chlorides into crystalline amide derivatives suitable for quasi-racemate studies also presented a problem in that application of the usual thionyl chloride method for preparing the intermediate acid chloride engendered cleavage of the benzyl ether function. This problem was circumvented by use of the procedure of Adams and Ulich,[15] wherein the acid chloride intermediates were prepared by adding the dry sodium salts of the enantiomeric acids to a slight excess of oxalyl chloride in benzene. A change in the sign of rotation accompanied the conversion of each acid into the amide enantiomers corresponding to VIb (Table I).

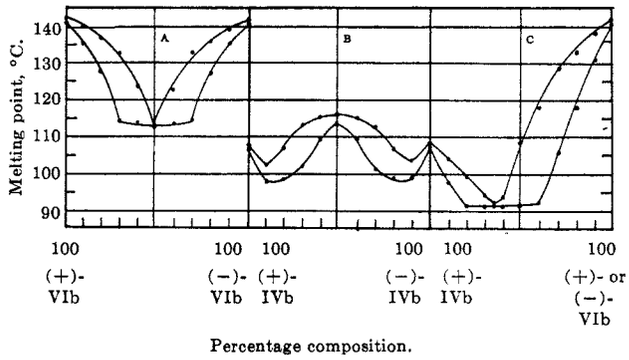


Figure 1.—Melting point–composition diagrams for enantiomers of O-benzylatrolactamide (A), 2-phenyl-2-benzylmercaptopropanoamide (B), and mixtures of each (C).

Despite mixture melting point evidence for a racemic compound between the enantiomers of atrolactic acid,[12] the melting point diagram for the enantiomers of O-benzylatrolactamide (VIb) (Figure 1A) gave evidence only for a racemic mixture. The enantiomers of 2-phenyl-2-benzylmercaptopropanoamides (IVb), on the other hand, showed by their mixture melting point

(13) W. A. Pryor, "Mechanisms of Sulfur Reactions," McGraw-Hill Book Co., Inc., New York, N. Y., 1962, p 76 ff.

(14) S. Imaizumi, *Nippon Kagaku Zasshi*, **81**, 627 (1960); *Chem. Abstr.*, **56**, 402*b* (1962).

(15) R. Adams and L. H. Ulich, *J. Am. Chem. Soc.*, **42**, 605 (1920).

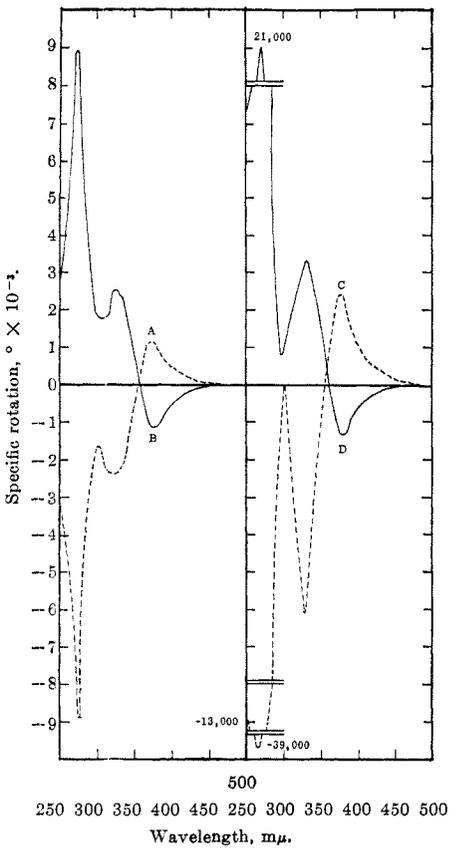
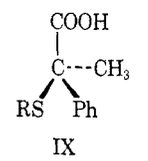


Figure 2.—Optical rotatory dispersion of N,N-diethylaminothiocarbamides derived from (+)- (A) and (−)-2-phenyl-2-benzylmercaptopropanoic (B) acids and from O-benzyl-(*S*)-(+)- (C) and O-benzyl-(*R*)-(−)-atrolactic acids (D).

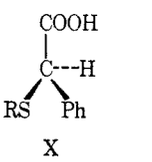
behavior (Figure 1B) a "strong tendency"[11b,16] to form a racemic compound, and might therefore be considered likely candidates for participation in quasi-racemate formation. While the direct configurational correlation of O and S analogs by the quasi-racemate method generally fails owing to the differing bulk of O and S atoms,[11] and "third-party" correlations involving $-CH_2-$ analogs must usually be applied,[11] the dominant tendency toward racemic compound formation shown by (+)- and (−)-IVb, as well as the hopefully overriding bulk of the remaining groups (Ph, Me, $PhCH_2$) of both molecules, led us to look for quasi-racemate formation between (+)-IVb and the enantiomers of VIb. This expectation, however, was not realized. As seen in Figure 1C, melting point diagrams of (+)-IVb and either enantiomer of VIb were identical and indicated only a solid solution of the two components, with perhaps simple eutectic behavior between 20 and 60% (+)-IVb. An identical melting point diagram was obtained for (*S*)-(−)-VIb and (−)-IVb. Thus no evidence for quasi-racemate formation was noted. The physical properties of the amides and acid precursors involved in these studies are summarized in Table I.

This approach having failed, configurational correlations between (*R*)-(−)-VIe and the enantiomers of IVa were next sought by means of optical rotatory dispersion measurements. In 1962 Djerassi and coworkers[17] studied the anomalous rotatory dispersion curves of a number of N,N-disubstituted N′-acylthiourea derivatives analogous to VIII, obtained from (*S*)-(+)-hydratropic acid and other optically active acids of known absolute configuration. The sign and magnitude of the Cotton effect of such acylthioureas, associated with "the interaction between the partially unshielded nuclei of the various substituents and the electrons involved in the 340-mμ transition of the C=S chromophore,"[17] proved fortunately to be correlatable with absolute configuration. It was found in general that, as with the (*S*)-hydratropyl derivative VIII, a negative Cotton effect was associated with acylthioureas from acids having the *S* configuration, while a positive Cotton effect was indicative of the *R* configuration. Similar correlations have been made more recently on thionamide derivatives of carboxylic acids.[18] Cotton effect studies on such derivatives of the acids IVa and VIe thus appeared promising as a means of deducing their stereochemical relationship.

The N,N-diethylaminothiocarbamide (DEATC) derivatives, analogous to VIII, of a number of the carboxylic acids in Table I were prepared by the previously described[17] reaction of the corresponding acyl halide with potassium thiocyanate, followed by diethylamine. The products were generally reddish oils which, however, were obtained chromatographically homogeneous and which gave acceptable elemental analyses. The DEATC of O-benzyl-(*R*)-(−)-atrolactic acid (VIe) derived from (*R*)-(−)-atrolactic acid (VIa) proved to have a negative Cotton effect (Figure 2D), while that of the enantiomeric O-benzyl-(*S*)-(+)-atrolactic acid showed an essentially equal and opposite positive Cotton effect (Figure 2C). Similarly, the DEATC of (−)-2-phenyl-2-benzylmercaptopropanoic acid ((−)-IVa) showed a negative Cotton effect (Figure 2B), while the DEATC of (+)-IVa again displayed the expected equal and opposite positive Cotton effect (Figure 2A). Negative Cotton effects were also displayed by the DEATC derivatives of both (−)-2-phenyl-2-phenylmercaptopropanoic acid ((−)-I) (Figure 3A), and the recently described[19] O-benzyl-(*R*)-(−)-mandelic acid (Vb) (Figure 3B). In view of the straightforward correlations noted by Djerassi[17] between the Cotton effect curves and absolute configurations of such DEATC derivatives, we believe that the above results demonstrate unequivocally that the levorotatory enantiomers of 2-phenyl-2-phenylmercapto- ((−)-I) and 2-phenyl-2-benzylmercaptopropanoic acids ((−)-IVa) each possess the *R* absolute configuration IX, similar to the *R* absolute configuration X, recently established[19] for the levorotatory



IX



X

α-phenylmercapto and α-benzylmercapto thio ethers derived from mandelic acid. The negative Cotton effects observed for the DEATC derivatives of both O-benzyl-(*R*)-(−)-atrolactic and O-benzyl-(*R*)-(−)-mandelic[19] acids provide yet another confirmation of

(16) K. Pettersson, *Arkiv Kemi*, **10**, 283 (1956).
(17) C. Djerassi, K. Undheim, and A. Weidler, *Acta Chem. Scand.*, **16**, 1147 (1962).
(18) J. V. Burakevich and C. Djerassi, *J. Am. Chem. Soc.*, **87**, 51 (1965).
(19) W. A. Bonner, *J. Org. Chem.*, **32**, 2496 (1967).

previous conclusions[5-10,20] as to the configurational similarity of (−)-atrolactic and (−)-mandelic acids.

It should be noted that in Djerassi's studies[17] a negative Cotton effect was associated with DEATC derivatives of the *S* configuration, while in our present observations a negative Cotton effect is indicative of the *R* configuration. In later rotatory dispersion studies of N-methylthionamide derivatives,[18] on the other hand, a negative Cotton effect was observed for *R* and a positive Cotton effect for *S* configuration acids containing only carbon and hydrogen atoms on the asymmetric center closest to the −C(=S)NHMe chromophore. These differences emphasize to us the requirement that such configurational correlations on the basis of Cotton effects be restricted to systems of reasonably close structural similarity, as in Mosher's recent configurational establishments[21] of optically active α-alkylphenylacetic acids by this method. The gross structural differences between our phenylmercapto-, benzylmercapto- and benzyloxy-DEATC derivatives and those studied previously by Djerassi[17] appear to us probably accountable for the opposite Cotton effects observed for DEATC derivatives of the same configuration among the two classes of acids in question. In addition, it has already been well emphasized[17,18] that the arbitrary conventions of the Cahn–Ingold–Prelog *R* and *S* system of configurational designation[22] may require that a small heteroatom at the asymmetric center take precedence over a much bulkier alkyl or aryl substituent. That is, *R* and *S* configurational notation does not necessarily reflect the intrinsic steric, electronic, or conformational features of the molecule, whose interplay determines the sign of the Cotton effect. Clearly such considerations are the basis of the above apparent "discrepancy" between our Cotton effect configuration observations and those of Djerassi.[17]

We are now in a position to answer the original question which prompted this study. On the basis of the above, the levorotatory sulfone amide (−)-IIa, derived from (*R*)-(−)-I, must also possess the *R* configuration analogous to IX. Its Raney nickel desulfuration[2] to produce (*R*)-(−)-hydratropamide (IIIa) is clearly attended by Walden inversion, the position of H in the product being opposite that of $PhSO_2$ in the precursor. The originally postulated[2] inversion of configuration during this reaction, based on limited "rule of rotational shift" data, is thus confirmed. The apparent "anomaly" of an *R* configuration substrate reacting with inversion to produce an *R* configuration product is, of course, a consequence of the arbitrary conventions of the Cahn–Ingold–Prelog notation[22] discussed above.

Our above-mentioned inability to prepare methyl O-benzylatrolactate by the procedure of Imaizumi[14] prompted us further to reinvestigate the optical course of benzyl ether hydrogenolysis with Raney nickel, previously reported[14,23] to proceed with retention of configuration. If, as seemed possible, Imaizumi's ethyl O-benzyl-(*S*)-(−)-atrolactate[14] substrate, an oil,

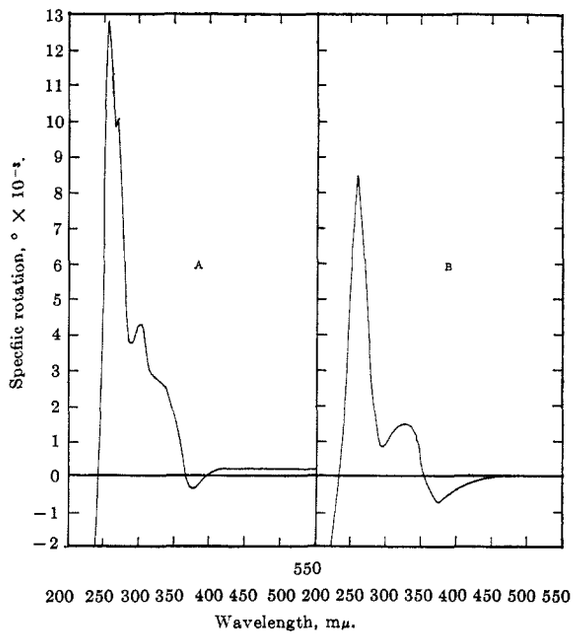


Figure 3.—Optical rotatory dispersion of N,N-diethylaminothiocarbamides derived from (−)-2-phenyl-2-phenylmercaptopropanoic (A) and O-benzyl-(*R*)-(−)-mandelic acids (B).

were contaminated with unbenzylated ester, one would not be in a position to assess accurately the stereochemical course of benzyl ether hydrogenolysis, since ethyl (*S*)-(+)-atrolactate is known[24] to yield ethyl (*R*)-(−)-hydratropate, without inversion, on Raney nickel hydrogenolysis.

A more definitive answer to the stereochemistry of benzyl ether hydrogenolysis might be obtained by the use of one of our crystalline enantiomers of O-benzylatrolactamide, and such an experiment was therefore undertaken. When O-benzyl-(*S*)-(−)-atrolactamide, the enantiomer of VIb, $[\alpha]^{25}D$ −13.8° (Me_2CO), was heated with excess Raney nickel in refluxing ethanol during 5 hr, a quantitative yield of (*R*)-(−)-hydratropamide (IIIa), $[\alpha]D$ −38.8° (EtOH), was obtained. Clearly this hydrogenolysis proceeded with retention of configuration and, on the basis of $[\alpha]^{25}D$ +46.5° (EtOH)[16] for the rotation of the enantiomeric (*S*)-(+)-amide, the product was 84% optically homogeneous. The conclusions of Imaizumi were thus confirmed.

Our previous estimates[2] of the optical purity of the hydratropamide samples obtained on reductive desulfuration were based on $[\alpha]^{25}D$ ±28.5° (75% EtOH) for this product, in agreement with the value reported by Levene and co-workers.[25] More recently Pettersson[16] has reported $[\alpha]^{25}D$ ±46.5° (EtOH) for the optically pure hydratropamides. Correcting for this higher value, as well as for the solvent change (*cf.* Experimental Section), we must revise our previous estimate of the optical course of sulfone desulfuration to the effect that (*R*)-(−)-2-phenyl-2-benzenesulfonylpropanoamide ((−)-IIa) is hydrogenolyzed with inversion of configuration, but to a (*R*)-(−)-hydratropamide product of only 52% optical homogeneity.

(20) T. R. Emerson, D. F. Ewing, W. Klyne, D. G. Neilson, D. A. V. Peters, L. H. Roach, and R. J. Swan, *J. Chem. Soc.*, 4007 (1965).
(21) C. Aaron, D. Dull, J. L. Schmiegel, D. Jaeger, Y. Ohashi, and H. S. Mosher, *J. Org. Chem.*, **32**, 2797 (1967).
(22) R. S. Cahn, C. K. Ingold, and V. Prelog, *Experientia* **12**, 81 (1956).
(23) S. Mitsui and S. Imaizumi, *Bull. Chem. Soc. Japan*, **34**, 774 (1961).
(24) W. A. Bonner, J. A. Zderic, and G. A. Casaletto, *J. Am. Chem. Soc.*, **74**, 5086 (1952).
(25) P. A. Levene, L. A. Mikeska, and K. Passoth, *J. Biol. Chem.*, **88**, 27 (1930).

Experimental Section

2-Phenyl-2-phenylmercaptopropanoic Acid (I).—Ethyl 2-phenyl-2-phenylmercaptopropanoate was prepared as previously described[2] by the action of sodium phenyl mercaptide in ethanol on ethyl 2-chloro-2-phenylpropanoate. When the former ester was hydrolyzed by refluxing with 10% aqueous sodium hydroxide, a clear yellow oil resulted which crystallized spontaneously. In recrystallizing the crude product from 3:10 benzene–ligroin, two crystalline forms were obtained, coarse prisms (mp 101–103°, 88%) and feathery needles (mp 140–150°, 12%). These were separated mechanically. Purification of the former afforded the known 2-phenyl-2-phenylmercaptopropanoic acid, mp 103.5–104°, whose nmr spectrum accorded with the supposed structure: methyl protons, singlet at 1.80 ppm; aromatic protons, complex multiplet at 7.25 ppm; carboxyl proton, singlet at 11.5 ppm (tetramethylsilane standard; $CDCl_3$; Varian A-60 spectrometer). The minor product, recrystallized from 1:20 acetone–ligroin, showed mp 145–146°, resolidification, and remelting (decomposition) at 154–154.5°. It was presumed to be 2-phenyl-3-phenylmercaptopropanoic acid (see below) and was not characterized further. Formation of the undesired by-product could be eliminated on conducting the above hydrolysis by vigorously stirring the crude ethyl ester (11.5 g) with 10% aqueous sodium hydroxide (150 ml) at 50° for 2.5 days, whereupon the mixture became homogeneous. The cooled solution was acidified and extracted with chloroform–ether (2:1; 200 ml). The extract was washed thoroughly with saturated sodium bicarbonate solution, then discarded. The bicarbonate solution was acidified, yielding an oil which solidified. The crude acid, mp 93–100°, was purified by recrystallization from 1:10 benzene–ligroin, 6.13 g (56%), whereupon it had mp 100–104°. It was resolved with the enantiomeric α-phenylethylamines as previously described.[2]

Methyl (*R*)-(−)-2-Phenyl-2-phenylmercaptopropanoate.—A sample of (*R*)-(−)-2-phenyl-2-phenylmercaptopropanoic acid[2] (85.3 mg) having mp 85.5–87°, $[\alpha]^{25}D$ −163° (*c* 2.66, EtOH), was dissolved in methanol (5 ml) and treated with sulfuric acid (0.25 ml), and the mixture was heated under reflux for 19 hr, then poured into ice water, treated with sodium chloride, and extracted into ether. Customary processing afforded 39.2 mg (44%) of the desired methyl ester, a clear, thick oil which was homogeneous on thin layer chromatography and had $[\alpha]^{25}D$ −94.6° (*c* 1.11, absolute EtOH).

Anal. Calcd for $C_{16}H_{16}O_2S$: C, 70.55; H, 5.92. Found: C, 70.36; H, 5.91.

Ethyl 2-Phenyl-2-benzylmercaptopropanoate (IVc).—Benzyl mercaptan (32 g) in ethanol (50 ml) was treated with a solution of sodium (6 g) in ethanol (200 ml), and the mixture was added to a solution of ethyl 2-chloro-2-phenylpropanoate (50 g) in chloroform (100 ml). The mixture was heated under reflux for 70 min, then was cooled, filtered, concentrated to *ca.* 200 ml, poured into water, and extracted with ligroin. The extract was washed with water, 10% aqueous sodium hydroxide, and water, then was dried ($MgSO_4$) and stripped of solvent. The residue, 47 g (66%), was distilled, bp 186–196° (3 mm), and then was redistilled prior to analysis, bp 183–187° (3 mm), $n^{20}D$ 1.5725.

Anal. Calcd for $C_{18}H_{20}O_2S$: C, 71.96; H, 6.71. Found: C, 71.95; H, 6.61.

2-Phenyl-2-benzylmercaptopropanoic Acid (IVa). Alkaline Hydrolysis at 100°.—The above ester (45.8 g) was heated in refluxing 10% sodium hydroxide solution for 6 hr. The solution was cooled, extracted with ligroin (discard), acidified with hydrochloric acid, and steam distilled until odorless, and the residue was extracted into ether. The extracts were washed with water, dried (Na_2SO_4), partially decolorized by filtration through Norit, and freed of solvent to yield 37 g (89%) of crude acid, an oil which later crystallized. Recrystallization from benzene–ligroin yielded 30.4 g of material, mp 81–105°.

During subsequent recrystallization two crystalline forms were observed: tufts of needles and coarse prisms. These were separated mechanically and each was purified by additional recrystallization. The needles, 8 g, mp 96–97°, were shown by their analysis and nmr spectrum to be 2-phenyl-3-benzylmercaptopropanoic acid. The signals for the $-CHCH_2-$ protons appeared as an ABX pattern located at 2.70, 3.12, and 3.65 ppm, with couplings J_{AB} = 13, J_{AX} = 6.8, and J_{BX} = 8.5 Hz; the two remaining benzylic protons, the aromatic protons, and the carboxyl proton comprised three singlets at 3.64, 7.22, and 11.3 ppm, respectively.

Anal. Calcd for $C_{16}H_{16}O_2S$: C, 70.56; H, 5.92; S, 11.77. Found: C, 70.54; H, 5.64; S, 11.88.

The coarse prisms above, recrystallized from 1:3 benzene–ligroin, proved to be the desired 2-phenyl-2-benzylmercaptopropanoic acid, mp 113–114°, as indicated by their analysis and nmr spectrum. The methyl protons showed as a singlet at 1.84 ppm; the nonequiv (hindered rotation) benzylic protons appeared as a pair of doublets at 3.63 and 3.85 ppm (J_{AB} = 12 Hz); the aromatic protons appeared as a complex multiplet between 7.17 and 7.25 ppm; and the carboxyl proton appeared as a singlet at 11.5 ppm.

Anal. Calcd for $C_{16}H_{16}O_2S$: C, 70.56; H, 5.92; S, 11.77. Found: C, 70.77; H, 5.85; S, 11.91.

Alkaline Hydrolysis at 50°.—Formation of the above undesired 2-phenyl-3-benzylmercaptopropanoic acid by-product could be eliminated by conducting the hydrolysis at lower temperature and avoiding the steam distillation. Ethyl 2-phenyl-2-benzylmercaptopropanoate (59.1 g) was mixed with 10% sodium hydroxide solution (350 ml) and ethanol (30 ml), and the mixture was stirred at 50° for 2.5 days. The homogeneous solution was cooled, acidified, and extracted twice with 200-ml portions of 2:1 ether–ligroin. The extract was washed with water and saturated sodium bicarbonate solution. The bicarbonate extract was acidified and the solid acid was collected, 37.5 g (70%). One recrystallization from benzene (30 ml) and ligroin (120 ml) yielded the pure acid, mp 113–114°.

Resolution of 2-Phenyl-2-benzylmercaptopropanoic Acid.—The above acid (28.6 g) in ethanol (35 ml) was converted to its (+)-α-phenylethylammonium salt by reaction with (+)-α-phenylethylamine (12.7 g) in ethanol (35 ml) and water (70 ml). Coarse crystals (16.3 g) formed and were recrystallized from ethanol (100 ml)–water (16 ml) and from ethanol (75 ml), resulting in 10.8 g of (+)-α-phenylethylammonium (−)-2-phenyl-2-benzylmercaptopropanoate, mp 174–174.5°, $[\alpha]^{27}D$ −54.4° (*c* 1.33, EtOH), unchanged on further recrystallization. The salt was shaken with dilute hydrochloric acid and extracted with benzene. The extract was dried and stripped of solvent, yielding 7.2 g of (*R*)-(−)-2-phenyl-2-benzylmercaptopropanoic acid ((−)-IVa), a thick oil, $[\alpha]^{24}D$ −46.5° (*c* 2.2, EtOH), which was characterized below as its crystalline amide.

Unresolved acid (20.7 g), similarly obtained, was recovered from the mother liquors of the above resolution, then converted to its (−)-α-phenylethylammonium salt with (−)-α-phenylethylamine (9.3 g) in hot ethanol (60 ml) and water (100 ml). The resulting salt was recrystallized three times as above, affording 10.6 g of (−)-α-phenylethylammonium (+)-2-phenyl-2-benzylmercaptopropanoate, mp 174–175°, $[\alpha]^{27}D$ +53.8° (*c* 1.24, EtOH). This was converted, as above, into free (*S*)-(+)-2-phenyl-2-benzylmercaptopropanoic acid ((+)-IVa), a viscous oil, $[\alpha]^{24}D$ +46.6° (*c* 2.3, EtOH).

(*S*)-(+)- and (*R*)-(−)-2-Phenyl-2-benzylmercaptopropanoamide.—The above (+) acid (5.05 g) was converted to its acid chloride (5.34 g, 98.5%) by refluxing with thionyl chloride (20 ml) for 30 min, then stripping the latter under vacuum. The oily product was treated with chilled ammonium hydroxide, and the crude amide product was dissolved in benzene, decolorized with Norit, and crystallized by adding ligroin to the point of incipient turbidity. The pure (*S*)-(+)-2-phenyl-2-benzylmercaptopropanoamide ((+)-IVb) (3.74 g, 75%) consisted of white needles, mp 107.5–108°, $[\alpha]^{28}D$ +14.5° (*c* 0.7, EtOH).

The above (*R*)-(−) acid was similarly converted in 75% yield into (*R*)-(−)-2-phenyl-2-benzylmercaptopropanoamide ((−)-IVb), mp 107.5–108°, $[\alpha]^{28}D$ −14.1°. (*c* 1.1, EtOH).

Anal. Calcd for $C_{16}H_{17}NOS$: C, 70.83; H, 6.32; N, 5.16; S, 11.79. Found (for (+)-amide): C, 71.17; H, 6.13; N, 5.15; S, 11.80. Found (for (−)-amide): C, 70.84; H, 6.03; N, 5.03; S, 11.80.

O-Benzylatrolactic Acid.—A 53% suspension of sodium hydride in mineral oil (4.37 g, 2.5 equiv; Metal Hydrides, Inc.) was stirred with butyl ether (60 ml) in a three-necked flask equipped with a mercury-sealed stirrer, a dropping funnel, and a reflux condenser to which was attached, through a $CaCl_2$ tube, a tube leading to an inverted 1000-ml graduate in a water trough. A solution of methyl atrolactate (6.95 g) in butyl ether (11 ml) was added dropwise with stirring over a 10-min period, and stirring was continued for another 10 min, after which 900 ml of hydrogen (95%) had been liberated. The mixture was stirred at 100° for 15 min, then treated dropwise with benzyl bromide (33 g, 5 equiv) at 100° over 15 min, stirred at 100° for 19 hr, and finally filtered through Celite. The filtrate was steam

distilled (250 ml) to remove butyl ether and excess benzyl bromide, and the residue was salted and extracted with ether. The extract was dried ($MgSO_4$) and stripped of solvent to yield a crude oily ester product (16.6 g) which was hydrolyzed by heating for 6 hr in a refluxing mixture of ethanol (40 ml) and 10% aqueous potassium hydroxide (80 ml). The hydrolysate was extracted with ether to remove neutral material (6.5 g; discard), then was acidified, salted, and extracted again with ether. The extract was dried ($MgSO_4$), decolorized with Norit, and freed of solvent to yield 9.36 g (94.7%) of thick, amber oil which slowly crystallized. Recrystallization from benzene (5 ml) and hexane (40 ml) afforded 8.2 g of white solid, mp 92.5–93.5°. A second recrystallization gave a sample having mp 93.5°, whose nmr spectrum showed three CH_3 protons (singlet, 1.88 ppm), two CH_2 protons (singlet, 4.43 ppm), ten aromatic protons (complex multiplet between 7.10 and 7.70 ppm), and one COOH proton (11.25 ppm).

Anal. Calcd for $C_{16}H_{16}O_3$: C, 74.98; H, 6.29; mol wt, 256.3. Found: C, 75.29; H, 6.46; neut equiv, 258.

An attempt was made to prepare the above product by the procedure of Imaizumi,[14] heating methyl atrolactate (10.8 g) in *t*-butyl alcohol (35 ml) containing sodium (1.3 g) at 100° for 1 hr, then adding benzyl bromide (7.7 g) and heating the mixture at 100° for 17 hr. The mixture was processed as above, yielding 5.12 g of crude ester product. Its hydrolysis, however, afforded an acidic product whose infrared spectrum was identical with that of atrolactic acid, indicating that little, if any, of the desired O-benzylation had occurred.

O-Benzylatrolactamide.—When an attempt was made to convert the above acid into its acid chloride using thionyl chloride (prior to ammonolysis), only benzyl chloride was obtained, indicating that the O-benzyl derivative had been cleaved. Adapting the procedure of Adams and Ulich,[15] therefore, the above acid (0.50 g) in ethanol (3 ml) containing a little water was titrated with dilute soldium hydroxide solution to the phenolphthalein end point. The solution was evaporated at 100° (air stream) and the solid sodium salt was finely pulverized and dried at 0.1 mm over P_2O_5. The dried solid was added in small portions with stirring to a solution of oxalyl chloride (0.25 ml, 1.5 equiv) and benzene (4 ml) in a flame-dried flask, and the mixture was heated under reflux for 15 min, then stripped of solvent under vacuum, treated with additional benzene (4 ml), and stripped again. The residue was treated with ether (3 ml) and chilled ammonium hydroxide by shaking the mixture thoroughly. The product was extracted into ether and processed as usual, affording 0.34 g (68%) of crude amide, an oil which quickly crystallized. Recrystallization was accomplished from benzene (0.75 ml) and hexane (6 ml), yielding pure O-benzylatrolactamide, mp 112.5–113°.

Anal. Calcd for $C_{16}H_{17}NO_2$: C, 75.27; H, 6.71; N, 5.49. Found: C, 75.00; H, 6.60; N, 5.72.

Methyl (*S*)-(+)- and (*R*)-(−)-Atrolactate.—Atrolactic acid was resolved into its (+) ($[\alpha]^{25}D$ +37.7° (*c* 1.2, EtOH)) and (−) enantiomer ($[\alpha]^{25}D$ −37.6° (*c* 1.2, EtOH)) by the procedure of Smith.[26] The enantiomers were converted into their methyl esters by direct esterification as previously described.[24] The (+) ester had $[\alpha]^{25}D$ +30.2° (neat), bp 99–100° (1 mm), $n^{25}D$ 1.5140, and d^{25}_{25} 1.131, while the (−) ester showed $[\alpha]^{25}D$ −30.3° (neat), bp 94–95° (0.1 mm), $n^{25}D$ 1.5150, and d^{25}_{25} 1.131. The values supplement those previously described in the literature.[5,24,27,28]

O-Benzyl-(*S*)-(+)- and O-Benzyl-(*R*)-(−)-atrolactic Acids (VIe).—The above methyl (*S*)-(+)-atrolactate (4.87 g) was converted into O-benzyl-(*S*)-(+)-atrolactic acid (4.78 g, 69%) in a manner exactly similar to that described for the above racemic counterpart of mp 93.5°. The (+) acid was a thick syrup, $[\alpha]^{27}D$ +4.1° (*c* 12.2, EtOH). Similar treatment of the above methyl (*R*)-(−)-atrolactate likewise afforded the desired O-benzyl-(*R*)- (−)acid VIe in 71% yield, a thick syrup, $[\alpha]^{25}D$ −3.7° (*c* 11.5, EtOH). The infrared spectra of each enantiomer were identical ($CHCl_3$) with that of the above racemic counterpart. The syrupy products were dried overnight at 25° (0.1 mm) over P_2O_5 prior to analyses.

Anal. Calcd for $C_{16}H_{15}O_3$: C, 74.98; H, 6.29. Found (for (+) enantiomer): C, 74.22, 74.23; H, 6.18, 6.15. Found (for (−) enantiomer): C, 74.67; H, 6.36.

O-Benzyl-(*S*)-(−)- and O-Benzyl-(*R*)-(+)-atrolactamide (VIb).—The above syrupy enantiomeric O-benzyl acids were converted into their crystalline amides, as before, *via* the acid chlorides prepared by the Adams and Ulich[15] procedure. A change in the sign of optical rotation accompanied the conversion of each acid to its amide. The above (*S*)-(+) acid afforded (70% yield) O-benzyl-(*S*)-(−)-atrolactamide, mp 141.5–142°, $[\alpha]^{25}D$ −13.8° (*c* 1.2, Me_2CO), while the (*R*)-(−) acid yielded (69%) the enantiomeric (*R*)-(+)-amide VIb, mp 141.5–142°, $[\alpha]^{25}D$ +13.1° (*c* 1.1, Me_2CO). Recrystallization of each was conducted in 1:4 acetone–hexane.

Anal. Calcd for $C_{16}H_{17}NO_2$: C, 75.27; H, 6.71; N, 5.49. Found (for (+) enantiomer): C, 75.50; H, 6.55; N, 5.48. Found (for (−) enantiomer): C, 75.36; H, 6.73; N, 5.47.

N,N-Diethylaminothiocarbamides.—The above enantiomeric O-benzyl ethers and α-mercapto derivatives derived from atrolactic acid, as well as the recently described[19] O-benzyl-(*R*)-(−)-mandelic acid, were converted into their N,N-diethylaminothiocarbamide (DEATC) derivatives by conversion to the acid chloride, followed by reaction first with potassium thiocyanate, then with diethylamine, according to the procedure of Djerassi, *et al.*[17] The intermediate acid chloride was prepared by the above Adams and Ulich procedure[15] for the O-benzyl acids and by the use of thionyl chloride for the α-mercapto acids. The resulting derivatives were recrystallized from ligroin when solid and dried under vacuum over P_2O_5 when oils, prior to analyses and rotatory dispersion measurements.[29] The latter were conducted in dioxane solution using a Jasco ORD-UV-5 optical rotatory dispersion recorder (Japanese Spectroscopic Co., Ltd., Tokyo), and are presented in Figures 2 and 3. The following physical constants and analyses were noted for the DEATC derivatives studied.

The (+)-DEATC derivative of (*R*)-(−)-2-phenyl-2-phenylmercaptopropanoic acid had mp 90.7–91.7°, $[\alpha]^{30}D$ +106° (*c* 0.7, EtOH), negative Cotton effect (Figure 3A).

Anal. Calcd for $C_{20}H_{24}N_2OS_2$: C, 64.50; H, 6.50; N, 7.52; S, 17.18. Found: C, 64.79; H, 6.62; N, 7.33; S, 16.90.

The (+)-DEATC derivative of (*R*)-(−)-2-phenyl-2-benzylmercaptopropanoic acid was an oil, $[\alpha]^{28}D$ +20.2 °(*c* 2.6, EtOH), negative Cotton effect (Figure 2B).

Anal. Calcd for $C_{21}H_{26}N_2OS_2$: C, 65.24; H, 6.78; N, 7.25; S, 16.59. Found: C, 65.69; H, 6.74; N, 6.91; S, 16.32.

The (−)-DEATC derivative of (*S*)-(+)-2-phenyl-2-benzylmercaptopropanoic acid was an oil, $[\alpha]^{29}D$ −19.1° (*c* 11.0, EtOH), positive Cotton effect (Figure 2A).

Anal. Calcd for $C_{21}H_{26}N_2OS_2$: C, 65.24; H, 6.78; N, 7.25; S, 16.59. Found: C, 64.96; H, 6.80; N, 7.03; S, 16.44.

The (+)-DEATC derivative of O-benzyl-(*R*)-(−)-atrolactic acid (VIe) was an oil, $[\alpha]^{25}D$ +34° (*c* 2.1, EtOH), negative Cotton effect (Figure 2D).

Anal. Calcd for $C_{21}H_{26}N_2O_2S$: C, 68.13; H, 7.07; N, 7.56; S, 8.65. Found: C, 68.05; H, 7.09; N, 6.94; S, 7.93.

The (−)-DEATC derivative of O-benzyl-(*S*)-(+)-atrolactic acid was an oil, $[\alpha]^{25}D$ −40° (*c* 1.9, EtOH), postive Cotton effect (Figure 2C).

Anal. Calcd for $C_{21}H_{26}N_2O_2S$: C, 68.13; H, 7.07; N, 7.56; S, 8.65. Found: C, 67.44; H, 7.03; N, 7.34; S, 8.22.

The (−)-DEATC derivative of O-benzyl-(*R*)-(−)-mandelic acid[19] was an oil, $[\alpha]^{25}D$ −2.9° (*c* 2.2, Me_2CO), negative Cotton effect (Figure 3B).

Anal. Calcd for $C_{20}H_{24}N_2O_2S$: C, 67.38; H, 6.78; N, 7.86; S, 8.99. Found: C, 68.40; H, 6.81; N, 6.83; S, 7.49 (sample somewhat impure).

The (−)-DEATC derivative of (*R*)-(−)-α-benzylmercaptophenylacetic acid, $[\alpha]^{25}D$ −162°, mp 91.5–92°,[19] was a red oil which slowly solidified, $[\alpha]^{25}D$ −5.4° (*c* 1.5, dioxane). Ether solutions of this product were washed several times with cold sodium bicarbonate solution before a homogeneous (thin layer chromatography) product was obtained. ORD measurement unexpectedly produced a plain dispersion curve for this substance.

Anal. Calcd for $C_{20}H_{24}N_2OS_2$: C, 64.48; H, 6.49; N, 7.52; S, 17.21. Found: C, 64.50; H, 6.61; N, 7.28; S, 17.24; Ash, 1.73.

Melting Point-Composition Diagrams.—The melting point–composition diagrams in Figure 1 were obtained as follows. Each component (30.0 mg) was dissolved separately in acetone (1.00 ml). Nine small, sawed-off test tubes were placed in a

(26) L. Smith, *J. Prakt. Chem.*, [2] **84**, 743 (1911).
(27) A. McKenzie and A. Ritchie, *Ber.*, **23**, 7013 (1937).
(28) D. J. Cram and K. R. Kopecky, *J. Am. Chem. Soc.*, **82**, 2748 (1959).

(29) We are indebted to Mrs. Ruth Records for our ORD measurements, and to Messrs. E. Meier and J. Consul for all of our microanalyses.

row, and into the first was added, *via* micropipet, one drop, the second two drops, the third three drops, etc., of the first solution, then into the first tube nine drops, the second eight drops, the third seven drops, etc., of the second solution. The ten-drop mixtures were evaporated to dryness at aspirator pressures in a desiccator, and each residue was ground and powdered intimately, with a glass rod, then dried at 0.1 mm over P_2O_5 for several hours. Melting ranges were determined in capillary tubes in a Thomas–Hoover "Unimelt," with a heating rate of *ca.* 0.5°/min during melting. The onset and completion of melting was frequently difficult to estimate, especially when the range was large. With some practice, however, a reproducibility of ±0.5 to 1.0° was generally achievable in duplicate determinations of each set of diagrams.

Raney Nickel and O-Benzyl-(*S*)-(−)-atrolactamide.—A mixture of the above levorotatory amide (0.25 g), Raney nickel catalyst (8 g), and absolute ethanol (25 ml) was heated under reflux for 5 hr, then cooled and filtered with a sintered-glass funnel, and the residual catalyst was rinsed with ethanol. The filtrate was stripped of solvent to yield 0.15 g (100%) of white solid. This was recrystallized from a mixture of benzene (1 ml) and hexane (5 ml), producing 0.12 g of shining white platelets, mp 93.5–94.5°, $[\alpha]_D^{28}$ −35.3° (*c* 1.24, 75% EtOH). Another recrystallization, with intermediate filtration through a Norit bed, gave a sample having mp 94.5–95°, $[\alpha]^{25}D$ −37.4° (*c* 1.44, 75% EtOH) and $[\alpha]^{25}D$ −41.2° (*c* 0.85, absolute EtOH), whose infrared spectrum in $CHCl_3$ solution was identical in all respects with that of authentic hydratropamide. The present product is 88% optically homogeneous, based on $[\alpha]D$ ±46.5° for optically pure hydratropamide.[16] The rotations of the above product in absolute ethanol and 75% ethanol are in a ratio of 1.10:1. This ratio has been used to correct the rotations of our previous hydratropamide samples[2] from 75% ethanol to absolute ethanol in order to make the corrected estimates of the optical purity of these earlier samples noted above.

Registry No.—I, 13479-08-8; (−)-I (+)-DEATC derivative, 13448-64-1; (+)-IVa, 13448-65-2; (+)-IVa (−)-DEATC derivative, 13473-45-5; (−)-IVa, 13448-66-3; (−)-IVa (+)-DEATC derivative, 13448-67-4; (+)-IVb, 13448-68-5; (−)-IVb, 13448-69-6; IVc, 13448-70-9; VIb, 13448-71-0; VIe, 13448-72-1; VIe (+)-DEATC derivative, 13448-73-2; *O*-benzyl-(*S*)-(+)-atrolactic acid, 13448-74-3; O-benzyl-(*S*)-(+)-atrolactic acid (−)-DEATC derivative, 13448-75-4; O-benzyl-(*S*)-(−)-atrolactamide, 13448-76-5; methyl (*R*)-(−)-2-phenyl-2-phenylmercaptopropionate, 13448-77-6; (+)-α-phenylethylammonium (−)-2-phenyl-2-benzylmercaptopropionate, 13448-78-7; (−)-α-phenylethylammonium (+)-2-phenyl-2-benzylmercaptopropionate, 13448-79-8; methyl (*S*)-(+)-atrolactate, 13448-80-1; methyl (*R*)-(−)-atrolactate, 13448-81-2; (*R*)-(−)-α-benzylmercaptophenylacetic acid (−)-DEATC derivative, 13479-09-9; O-benzyl-(*R*)-(−)-mandelic acid (−)-DEATC derivative, 13448-82-3; O-benzyl-(±)-atrolactic acid, 13448-83-4; O-benzyl-(±)-atrolactamide, 13448-84-5; (±)-2-phenyl-2-benzylmercaptopropanoic acid, 13448-85-6; 2-phenyl-3-benzylmercaptopropanoic acid, 13448-86-7.

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Tautomerism of 2-Substituted Benzo[*b*]thiophenes. Ultraviolet Spectral Correlation of Tautomer Structure with Aromaticity[1a,b]

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Stepwise methylation of *o*-benzylthiophenylacetonitrile (**2**) conveniently affords a route to the 2-amino-3-methylbenzo[*b*]thiophene (**6**) and the more critically significant dimethyliminodihydrobenzo[*b*]thiophene (**1**). Study of the infrared and nuclear magnetic resonance spectra of **1** and **6** and derivatives in comparison with related compounds previously obtained provides further evidence for imino–amino structural assignments, as well as a firm basis for the assignment of the hitherto uncertain 2-oxygen-substituted derivatives. Strategic confirmation of the 2-aminobenzo[*b*]thiophene structure was accomplished by comparison of the acetyl derivative of **6** with the same material derived from the corresponding 2-nitro intermediate. The synthesis of **6** and **1** in excellent yield further demonstrated the utility of anhydrous aluminum bromide in removal of a masking benzyl group from the sulfur function in the ring tautomeric heterocyclization reaction. Various studies of tautomer chemistry involving Schiff base, hydrochloride, and disulfide formation are described. Convenient differentiation of tautomer structures was discovered possible by correlation of ultraviolet spectral properties with the aromaticity of the ring system.

A major type of tautomerism in heterocyclic systems is that involving proton location between an annular carbon atom and an atom adjacent to the ring.[2] 2-Aminobenzo[*b*]thiophene, recently synthesized in this laboratory,[3] is an example. An opportunity to accumulate persuasive spectroscopic evidence on the tautomerism of these systems was seen in the methylated series **3a** → **6** and **4a** → **1** (Scheme I). Special interest centered on the dimethyliminodihydrobenzo[*b*]thiophene (**1**), as in this case the amino structure, of course, is precluded by methyl substitution at position 3, thus making possible unequivocal assignments consistent with the imino function.

It had been hoped that the synthesis of **1** would be easily accomplished by the appropriate dialkylation of **2**. A procedure for dialkylation of phenylacetonitrile described by Bloomfield[4] unfortunately led to a mixture of mono- and dimethylated derivatives (**3a** and **4a**). However, possible use of benzyl chloride as an alkylating agent suggested a convenient product separation as a consequence of a possibly wider margin in boiling

(1) (a) Presented before the Division of Organic Chemistry at the 150th Meeting of the American Chemical Society, Pittsburgh, Pa., April 1966. (b) For paper IV on Tautomerism, see G. W. Stacy and P. L. Strong, *J. Org. Chem.*, **32**, 1487 (1967). (c) National Science Foundation Summer Fellow, 1963; National Science Foundation Cooperative Fellow, 1963–1964. (d) In part from the Ph.D. Thesis of T. E. Wollner, Washington State University, June 1965.

(2) A. R. Katritzky, *Advan. Heterocyclic Chem.*, **1**, 313, 347, 328 (1963).

(3) (a) G. W. Stacy, F. W. Villaescusa, and T. E. Wollner, *J. Org. Chem.*, **30**, 4074 (1965); (b) the enclosure denotes the stable tautomer of the various possibilities under discussion.

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