

Separation of an Enantiomorph and Its Racemate by Sublimation

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Partially resolved α -ethylbenzylphenyl sulfide² was found to experience loss of optical activity upon subjection to reduced pressure in a vacuum desiccator at room temperature. Quantitative studies have shown that such racemization is due to sublimation of the enantiomorph in excess, present in small concentration but of high specific activity, leaving behind the less volatile racemate. Some discussion is given to the significance these observations may have for the nature of racemates. The possibility that the sublimation method may be generally applied for the separation of partially resolved compositions is also considered.

Interest in this subject originated with an observation in our laboratory² during the preparation of optically active α -ethylbenzylphenyl sulfide for chlcrlinoly-sis studies. On pumping an active sample overnight in a vacuum desiccator over drying agents like P₂O₅, the activity of the sample was found to have decreased substantially. Initially, consideration was given to the possibility that the sample had experienced racemization through the agency of the electrophilic surface provided by the P₂O₅ desiccant. Subsequent examination of the possible reversible formation of ionradicals under these conditions disclosed that this was a very unlikely course of racemization. It soon became clear that the optically active component of the sample was present in relatively small amounts but was of very high specific activity; thus it was being lost through volatilization while leaving behind the major constituent of the mixture, namely, an inactive racemic compound which was stable at the relatively low temperature of the vacuum drying operation.

Generally speaking, racemic compounds are considered to exist only in the liquid and solid states. It has been quite conclusively shown that in the gaseous state racemic compounds are usually, if not always, dissociated.³ There is also some controversy in the literature as to whether liquid racemates or racemic compounds in solution actually exist. Campbell³ concludes that the series of *dl*-tartaric acid esters form liquid racemates and that these are actually less associated than the corresponding active esters on the basis of physical constants. However, cryoscopic data has failed to yield any "double" molecular weights for racemates.^{4,5} Dunston and Thole⁶ found that the degree of dissociation of *dl*-mandelic acid is less in amyl acetate than in pyridine or water as solvent on the basis of viscosity measurements. Singh and Perti^{7a} concluded that the *dl*-camphor- β -sulfonic acid racemate is stable in both the fused and dissolved state on the basis of the shape of the Roozeboom melting point-composition diagram.^{7b} On the other hand, Rumeau⁸ deduced that racemates do not exist in solution, especially dilute ones, on the basis of his velocity of crystallization data.

The forces bonding the racemate constituents together may be of varied nature and have been the subject of some speculation. Ross and Somerville,⁹ for example, have postulated an electrostatic interaction. Eliel and Kofron¹⁰ have presented evidence of a form of intermolecular hydrogen bonding. The spectra of racemates and pure enantiomers have been investigated rather extensively in this connection. Singh and co-workers^{11,12} have claimed that the ultraviolet absorption spectra of some *dl*-*p*-X-anilino camphorsulfonates have slightly different absorption maxima and molecular extinction coefficients and show a fewer number of absorption maxima than their corresponding *d* forms. The evidence of infrared spectra have been invoked¹⁰ to support the proposal that intermolecular hydrogen bonding is much more important in crystals of a racemic compound than in the crystals of the constituent enantiomorphs. A somewhat different interpretation was conferred in the infrared spectra of *d*-, *l*-, and *dl*-*meso*-tartrate salts by Duval and Lecomte.¹³

Clearly, it has been well established that racemic compounds differ in some of their physical properties from those of the constituent enantiomorphs and this fact has been used frequently for purposes of enantiomorph separation in the solid state. For example, Neidel and Liebig¹⁴ have isolated (+)-*N*-acetyl- α -phenylethylamine from the racemate by repeated crystallization from 1:1 benzene-petroleum ether. On the other hand, Dupont and Desalbres^{15a} have reported the separation of active pinene from admixture with the *dl* liquid by simple distillation in a special apparatus. However, this result must be regarded with some doubt since even the highly efficient distillation assembly represented by gas-liquid partition chromatography (glpc) has never successfully been demonstrated to effect such separations. For example, racemic amino acids converted through derivatization to volatile diastereoisomers have been separated by gas chromatographic methods,^{15b} but it has never been claimed that an active component present in an excess of a racemic modification has been separated in this manner. The main reason for this is that the racemate would most likely dissociate extensively, if not completely, in the injection port region of the apparatus. It must be considered as quite unusual, therefore, when

(1) Abstracted in part from the thesis of D. P. Holster submitted in partial fulfillment of the M.S. degree requirements at the University of Delaware, June 1965.

(2) See P. S. Strilko, Ph.D. thesis, University of Delaware, June 1964.

(3) A. W. Campbell, *J. Chem. Soc.*, 1111 (1929).

(4) H. Gilman, "Organic Chemistry, An Advanced Treatise," Vol. 1, John Wiley and Sons, Inc., New York, N. Y., 1944, p 285.

(5) A. D. Mitchell and C. Smith, *J. Chem. Soc.*, 103, 489 (1915).

(6) E. A. Dunston and F. B. Thole, *ibid.*, 97, 1249 (1909).

(7) (a) B. K. Singh and O. N. Perti, *Proc. Indian Acad. Sci.*, 22A, 170 (1945). (b) See, however, H. Mauer, *Ber.*, 90, 307 (1957), for a thorough discussion of these considerations.

(8) G. Rumeau, *Compt. Rend.*, 196, 410 (1933).

(9) J. D. Ross and I. C. Somerville, *J. Chem. Soc.*, 2770 (1926).

(10) E. L. Eliel and J. T. Kofron, *J. Am. Chem. Soc.*, 75, 4585 (1953).

(11) B. K. Singh and M. K. P. Amma, *J. Sci. Ind. Res. (India)*, 16B, 486 (1957).

(12) B. K. Singh and B. S. Saxama, *J. Indian Chem. Soc.*, 35, 227 (1958).

(13) C. Duval and P. Lecomte, *Comp. Rend.*, 219, 483 (1944).

(14) F. Neidel and H. Liebig, *Ann.*, 42, 621 (1959).

(15) (a) G. Dupont and H. Desalbres, *Compt. Rend.*, 176, 1881 (1923).

(b) See, for example, E. Gil-Av, R. C. Sigler, G. Fishcer, and D. Nurok, *J. Gas Chromat.*, 51 (1966), and other references cited therein.

an enantiomorph can be volatilized free of its corresponding racemic modification.

"Resolution" by Sublimation.—Samples of partially active α -ethylbenzylphenyl sulfide were sublimed and the sublimate and residue optical activities were measured at definite time intervals. In most cases, the initial optical activity of the sublimate was found to have increased from that of the charged sample while that of the corresponding residue had decreased. That is to say, the material subliming initially had extraordinarily high activity compared to the charged sample, and, while successive portions of sublimed material showed a declining activity, in nearly all cases the sublimate manifested enhanced activity compared to the residue. Three separate studies of this resolution phenomenon were carried out with similar results. Two studies were done with (+)-sulfide and one with (–)-sulfide. The results are summarized in the accompanying tables.

Each of the sublimations were carried out at 35°, but, since very long intervals of time were involved, the control temperature occasionally drifted slightly from the set point. On one occasion (see Tables I and II and 48-hr entry on Table III) the slightly greater activity of the residue compared to the sublimate apparently could be correlated with an abnormally high temperature of the pot.

Given sufficient time of sublimation at 35° (85 hr, Table II) the residue was reduced to pure racemate. In this fashion from a composition of enantiomorph and racemate representing less than 12% of the (ultimate) activity of the pure enantiomorph approximately

TABLE I^a

| Time elapsed, hr | Accumulated total ^b | % sublimed, by wt ^c | [α] ^{25D} (EtOH), deg | |
|------------------|--------------------------------|--------------------------------|---|----------------------------|
| | | | Sublimate rotation, deg ^{d,e} | Rotation of remainder, deg |
| 18 | 0.2313 | 7.4 | –81.7 | –7.58 |
| 30 | 0.4688 | 7.6 | –16.25 | –4.22 |
| 42 | 0.6370 | 5.4 | –8.32 | –4.09 |
| 54 | 0.8901 | 8.1 | –5.37 | –4.26 |
| 67 | 1.0746 | 5.9 | –5.92 | –2.78 |
| Total sublimed | | 34.4 | | |

^a Initial activity of sulfide was [α]^{25D} –16.30° (EtOH); original weight was 3.123 g. ^b Grams of sulfide sublimed and collected. ^c In time interval. ^d Nonaccumulated. ^e An error of ca. $\pm 15\%$ inherent in the figures listed in this column is not unreasonable in view of the very high specific activity of the (excess) enantiomorph component and the mechanical difficulties involved in obtaining maximum recovery of the successive semisolid fractions from the cold finger of the sublimator.

TABLE II^{a,b}

| Time elapsed, hr | Accumulated total | % sublimed (by wt) | [α] ^{25D} (EtOH), deg | |
|------------------|-------------------|--------------------|---|----------------------------|
| | | | Sublimate rotation, deg | Rotation of remainder, deg |
| 12 | 0.2628 | 12.5 | +128.1 | ... |
| 24 | 0.4698 | 9.8 | +108.3 | ... |
| 36 | 0.5551 | 4.1 | +82.0 | +6.75 |
| 48 | 0.5894 | 1.6 | +60.5 | +4.70 |
| 60 | 0.6570 | 3.2 | +7.13 | +2.18 |
| 72 | 0.7454 | 4.2 | +3.24 | +3.20 |
| 85 | 0.7977 | 2.5 | +1.93 | +0.00 |
| Total sublimed | | 37.9 | | |

^a Initial activity of sulfide was [α]^{25D} +20.70° (EtOH); original weight was 2.102 g. ^b See Table I. Footnote b–e are the same in this table.

TABLE III^{a,b}

| Time elapsed, hr | Accumulated total | % sublimed (by wt) | [α] ^{25D} (EtOH), deg | |
|------------------|-------------------|--------------------|---|----------------------------|
| | | | Sublimate rotation, deg | Rotation of remainder, deg |
| 12 | 0.1784 | 2.6 | +131.0 | +7.27 |
| 24 | 0.2251 | 0.7 | +128.0 | +6.67 |
| 36 | 0.3353 | 1.6 | +42.2 | +1.84 |
| 48 | 0.4097 | 1.1 | +2.72 | +3.80 |
| 60 | 0.4785 | 1.0 | +6.90 | +2.92 |
| Total sublimed | | 7.0 | | |

^a Initial activity sulfide was [α]^{25D} +11.35° (EtOH); original weight was 6.9906. ^b See Table I. Footnotes b–e apply here also.

62% of the initial weight could be separated as pure racemate, along with the recovered 38% of sublimate possessing strongly enhanced optical activity.

A demonstration of the importance of low temperatures to the success of the separation and the necessity for maintaining the racemate in the crystalline state was achieved in the following manner. A sample of (+)- α -ethylbenzyl sulfide, [α]^{25D} +5.37, 0.80 g, was heated in the sublimator at 48° for 12 hr. At this temperature the sample was observed to be completely molten. It was found that, within the limits of experimental error, the sublimate, residue, and starting material had the same activity. About 30% of the original sample had sublimed under these conditions. On the other hand, the obvious lack of parallelism between the activity of the sublimate and that of the residue in the 35° sublimation suggests that separation of the original sample into its enantiomorph and racemate components was not perfect. In other words, at the chosen temperature of study (35°) some of the racemate is dissociated into its volatile constituents. Nevertheless, an extraordinary degree of enrichment in activity could be attained by this procedure; thus, the 12-hr sample in Table III represents enrichment from a starting level¹⁶ of about 6% optical purity to about 74%.

Among the various physical properties of active (131° rotation sample) and racemic materials that could be readily compared, only the melting point showed significant difference. The active material had a lower melting point (32–35° cor) compared to racemate (39–42° cor) and a mixture melting point showed some depression, but the actual magnitude was difficult to determine accurately because of the proximity to room temperature. Since both fusion temperature and volatility are related to the intercrystalline force, the differences in these physical properties that distinguish enantiomorph and racemic modifications are the only way of accounting for their separation through sublimation. Thus, both the enantiomorph and racemate displayed superimposable infrared spectra (1% in KBr), using a high resolution grating instrument in the effort to detect even the slightest distinctions. A similar result, of course, was observed in the comparison of ultraviolet spectra. It is quite apparent, therefore, that the cause of the differences does not arise from even the most subtle disparities in any aspects of bonding forces within the racemate or the enantio-

(16) This deduction is based on an independent determination of the activity of the pure enantiomorph (174.3°) by R. Alderson of these laboratories to be discussed in a future article.

morph, such as has been identified in one case by Eliel and Kofron.¹⁰

Conclusions and Recommendations.—The indications discussed above would tend to suggest that the racemic modification is the result of some kind of twinning of the enantiomorphous constituents in the unit cell of the crystal and the interaction energy is not very much greater than thermal energy levels near room temperature. However, this interaction is both different and greater than could be expected to result from solid solution or a solid-state conglomerate of the components, in which cases separation from excess enantiomorph on the basis of volatility near room temperature would not be possible.

It seems clear that we are dealing with a phenomenon originating in the forces that control crystal structure and crystal growth. Since these are also related to the factors that make possible enantiomorphous separation *via* fractional crystallization, an effort was made to determine which procedure afforded the most efficient separation. For this purpose a sample of the same optical activity as was used in a typical sublimation run (see Table III) was dissolved in a minimum amount of hexane; the solution was cooled to -25° . Each crop of slowly emerging crystals was separated; the residual solution was evaporated to one-half volume and returned to the cold chest for further crystallization. From the results summarized in Table IV, it appears that the racemic material is the less soluble in hexane.

TABLE IV^a
SEPARATION BY FRACTIONAL CRYSTALLIZATION

| Fraction | Wt recovd | % recovd | $[\alpha]_D^{25}$ (EtOH), deg |
|----------|--------------|-------------|----------------------------------|
| 1 | 3.334 | 65.0 | +1.51 |
| 2 | 0.711 | 14.0 | +4.66 |
| 3 | 0.281 | 5.5 | +15.32 |
| 4 | 0.038 | 1.1 | +18.40 |
| 5 | 0.0139 | 0.4 | +42.70 |

^a Starting material was 5.13 g of sulfide, $[\alpha]_D^{25} +11.35^{\circ}$, EtOH.

It is also very clear that the sublimation method is by far the more efficient, taking consideration of the largest yield of the active material obtainable in the form of its greatest purity. From the point of view of simplicity of handling and obviating the necessity of finding the most appropriate solvent, as behooves the use of fractional crystallization procedures, sublimation is again the method of choice whenever it can be applied. In general, the most favorable circumstances for its application would occur when (a) the enantiomorphs tend to form a racemate of relatively high resistance to thermal dissociation at convenient temperatures, (b) the enantiomorphs should have some volatility at temperatures at which the racemate is not extensively dissociated, or (c) the enantiomorphs may be converted to a more volatile derivative which possesses the properties (a and b) above. Some of the devices applied in mass spectrometry to increase volatility may also be attempted in the effort to realize the circumstances c; for example, the conversion of alcohols to trimethylsilyl ethers could be a resort that would increase vapor pressure of the enantiomorph without destroying the capability of racemate formation. Work presently in progress in our laboratories is directed toward this objective.

It is important to emphasize the potential utility of the sublimation method. It is obvious that one does not avoid the use of an asymmetric material or a partial asymmetric synthesis somewhere along the route of preparation, since the method does require that the substrate be at least partially resolved and available in the form of a composition of enantiomorph and racemate. Thus, where resolution through diastereomeric separations are incomplete (and this is quite a common occurrence in the author's experience), or where some of the newer methods of asymmetric synthesis can be applied, the sublimation approach to separation of the active component may be attempted without untoward difficulties.

The isotope dilution technique of determining enantiomeric purity, as developed by Graff, Rittenberg, and Foster^{17a} and applied somewhat later by Berson and Ben-Efraim,^{17b} requires separation of the pure racemate from a mixture with enantiomorph. This step often represents a difficulty which in certain cases (as defined above) may be circumvented by the use of the sublimation method. In this connection a suggestion by the Editor is gratefully acknowledged.

Experimental Section

Procedure for the Preparation of Partially Resolved α -Ethylbenzylphenyl Sulfide.—The general procedure is outlined in Scheme I.

Ethylphenylcarbinol.—This substance was prepared in the usual fashion and its physical properties agreed well with those reported in the literature: bp $106-108^{\circ}$ (18 mm), n_D^{20} 1.5208. Its resolution was carried out (as below) by a method similar to that reported previously.¹⁸

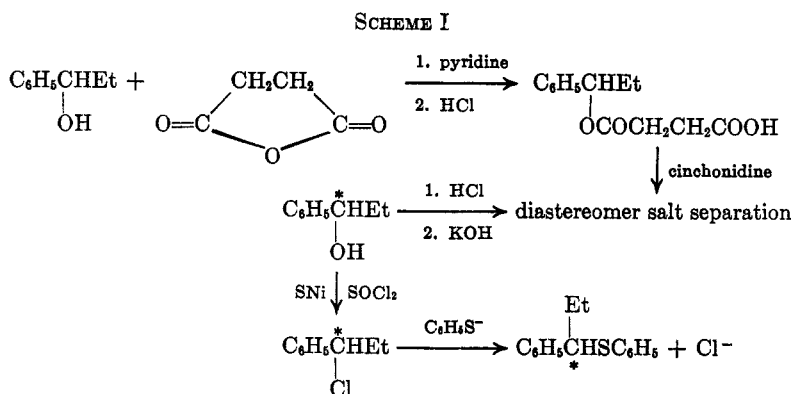
Preparation of the Half Acid Succinate.—A mixture consisting of 123 ml (0.9 mole) of ethylphenylcarbinol, 99 g (0.99 mole) of succinic anhydride, and 210 ml of anhydrous pyridine was stirred on a steam bath for 3.5 hr, care being taken to avoid moisture in the reaction medium. The cooled mixture was then poured into 350 ml of concentrated HCl over 1 kg of ice. After 45 min of stirring, the two-phase system was extracted with four 400-ml portions of ether. The combined extracts were washed with two 200-ml portions of water and dried over anhydrous Na_2SO_4 , and the solvent was stripped under vacuum. The crude half ester was used without further purification; the yield of crude varied in ten runs between 89 and 99% of theory.

Preparation of the Cinchonidine Salt and Resolution *via* Fractional Crystallization of the Diastereoisomers.—The crude half succinate ester (0.9 mole) was dissolved in 250 ml of boiling anhydrous chloroform (CP) and a 0.1 mole excess of cinchonidine alkaloid was added slowly (15 min) to the boiling solution. This was followed after 15 min by the addition of 2.5 l. of boiling anhydrous acetone. After cooling to about $25-30^{\circ}$ the excess unreacted cinchonidine was removed by filtration and the filtrate was allowed to stand for 3 days in the dark at room temperature. The cinchonidine salt of the (–) rotatory alcohol precipitated as fluffy white crystals which were separated from the supernatant and dried in a vacuum oven. It was recrystallized by dissolving in sufficient boiling chloroform and (again) adding 2.5 l. of boiling acetone. This solution afforded the best crystals upon being permitted to stand at room temperature for about 3 days, mp $159-162^{\circ}$.

The active alcohol was sequestered first by dissolving the salt in 600–800 ml of 15% HCl and extracting the half acid ester away from the protonated alkaloid with chloroform. The dried chloroform extracts were stripped of the solvent under vacuum and the residue was saponified by refluxing with an excess of 40% aqueous KOH for 18 hr. After neutralizing with dilute H_2SO_4 the free alcohol was extracted into pentane, and the

(17) S. Graff, D. Rittenberg, and G. L. Foster, *J. Biol. Chem.*, **133**, 745 (1940); (b) J. A. Berson and D. A. Ben-Efraim, *J. Am. Chem. Soc.*, **81**, 4088 (1959).

(18) R. H. Pickard and J. Kenyon, *J. Chem. Soc.*, **99**, 45 (1911).



combined extracts were washed with water and dried over K_2CO_3 . The solvent was removed under vacuum and the residual oil was vacuum distilled: bp $77\text{--}82^\circ$ (2.0 mm), n_{D}^{20} 1.5190, $[\alpha]_{\text{D}}^{20}$ ranged from -35.40 to -47.03° (acetone).

The active (+) rotatory alcohol was obtained from the supernatant liquids remaining when the salt of the (-) alcohol (half ester) initially precipitated. The same procedure as above was followed in effecting saponification and purification of the resulting alcohol. All of the (+) alcohol samples in a typical run were combined to give 147.5 g with n_{D}^{20} 1.5193 and $[\alpha]_{\text{D}}^{20}$ $+8.4^\circ$ (neat). Similarly all the (-) alcohol samples in a typical run could be combined to give 86.5 g with n_{D}^{20} 1.5188 and $[\alpha]_{\text{D}}^{20}$ -24.30° (neat).

Preparation of α -Chloropropylbenzene (Active and Inactive).—Ethylphenyl carbinol was added dropwise to a stirred vessel containing a 50% excess of thionyl chloride at 20° . The reaction mixture was stirred for an additional hour at 25° and the brought to 80° and held there for 5 min. The cooled material was then poured onto 300 g of crushed ice. The product was extracted with three 100-ml portions of ether; the combined extracts were neutralized with 5% NaHCO_3 solution, and then washed once more with distilled water. After drying, the solvent was flashed off under vacuum and the residual oil was distilled under high vacuum. The (-) rotatory alcohol (referred to above) showed activity $[\alpha]_{\text{D}}^{20}$ -37.20° in acetone; the (+) rotatory alcohol showed $[\alpha]_{\text{D}}^{20}$ $+13.4^\circ$, bp $88\text{--}93^\circ$ (14 mm), n_{D}^{20} 1.5208–1.5222 (chlorides).

Preparation of α -Ethylbenzylphenyl Sulfide (Active and Inactive).—Freshly cut sodium was treated with a 1.4 mole excess of absolute ethanol in anhydrous ether solution. An equimolar quantity of freshly distilled thiophenol was gradually added to the sodium ethoxide solution while the ether refluxed gently. The α -chloropropyl benzene was then added under reflux and stirring, which was continued for 12 hr while maintaining a blanket of oxygen-free nitrogen over the reaction surface. The ethanol was then distilled while the temperature was raised to 80° . The residue was now poured into 350 ml of ice water. The ivory-colored solid was collected at the pump, transferred to a flask, dissolved in hexane, and dried over CaCl_2 . The solution was treated with activated charcoal and then cooled in a refrigerator where white needles slowly formed. Upon filtration, evaporation, and further cooling, successive crops could be isolated which had varying activities: the (-) rotatory samples ranged in activity from -4.63 to -16.12° and the (+) rotatory samples from $+10.35$ to $+20.42^\circ$ (EtOH). The melting point of various fractions ranged from 40 to 44° ; the literature¹⁹ melting

point was 42° after recrystallization from 50% ethanol-water.

The Dependence of Optical Activity on Solvent.—The specific rotations of a sample of (+)-ethylphenylcarbinol were measured in five different media. In Table V are listed factors for inter-conversion of readings under these conditions.

TABLE V

| Solvent | Concn, g/100 ml | Obsd rotation, deg | Specific rotation, $[\alpha]_{\text{D}}^{20}$, deg | Conversion factor |
|---------------|-----------------|--------------------|---|-------------------|
| Neat | 6.253 | +0.0627 | +10.05 | 1.000 |
| Absolute EtOH | 5.927 | +0.0758 | +12.81 | 1.28 |
| Acetone | 6.905 | +0.1110 | +16.05 | 1.60 |
| Ether | 6.997 | +0.1360 | +19.45 | 1.94 |
| Pentane | 5.128 | +0.0725 | +14.16 | 1.41 |

The Dependence of Sulfide Activity on Concentration in Ethanol.—A number of solutions of a sample of (+)- α -ethylbenzylphenyl sulfide were prepared in absolute ethanol in the concentration range 0.392–7.968 g/100 ml. The specific rotations are shown in Table VI. Significant deviations are to be noted

TABLE VI

| Concn, g/100 ml | $[\alpha]_{\text{D}}^{20}$, deg | Concn, g/100 ml | $[\alpha]_{\text{D}}^{20}$, deg |
|-----------------|----------------------------------|-----------------|----------------------------------|
| 0.392 | +17.80 | 1.146 | +10.50 |
| 0.576 | +14.60 | 4.200 | +10.50 |
| 0.832 | +11.70 | 7.968 | +10.50 |

at low concentrations of the active substrate. Subsequent readings reported in this article were made in the range ca. 1.0–6.00 g/100 ml.

Registry No.—(+)- α -Ethylbenzylphenyl sulfide, 10299-86-2; (-)- α -ethylbenzylphenyl sulfide, 10299-87-3; cinchonidine salt, 10324-59-1; (+)-ethylphenylcarbinol, 613-86-5; (+)- α -chloropropylbenzene, 10299-90-8; (-)- α -chloropropylbenzene, 10316-10-6; (-)-ethylphenylcarbinol, 613-87-6; racemate of α -ethylbenzylphenyl sulfide, 10299-88-4.

(19) P. A. Briscoe, F. Challenger, and P. S. Duckworth, *J. Chem. Soc.*, 1763 (1956).