temperature for 5 hr; the mixture was concentrated and extracted with chloroform. The chloroform extract was washed, dried, and concentrated to leave light brown oil. The residue was chromatographed over alumina. Elution with ether gave 0.32 g of **18** as colorless oil, which proved to be identical with an authentic sample by ir comparison.

**Kinetic and Rate Constant Measurements.**—The rates of rearrangement of 2-(1-diethylphosphoroyl)benzyliden-3-benzyl-4-methyl-5-(2-benzoyloxy)ethyl-4-thiazoline (**19**) were measured by following the decrease of the intensity at 373.5 mμ, using a Hitachi EPS-3 spectrophotometer equipped with a thermostated cell holder. A solution containing 2.9 ml of $9.3 \times 10^{-1}$ *M* **10b** in 95% ethanol was prepared in 4 ml with 1-cm cuvettes and temperature equilibration. Reaction was initiated by the addition of 0.1 ml of temperature-equilibrated solution of $6.06 \times 10^{-2}$ *M* sodium hydroxide in 95% ethanol from a blow-out pipet, followed by rapid mixing with hands. The first reading of intensity was taken about 15 sec after the addition, and thereafter readings were taken at 10-sec intervals during 2 min, after which readings were taken at 30-sec intervals. All the plots of log ε against time were linear for at least 50 min. The rate constants were reproducible within ±4% of the average. The extinction coefficient of **19** at 373.5 mμ in $2 \times 10^{-3}$ *N* NaOH at 15° was obtained by extrapolating of the plot of log ε against time to the moment at which sodium hydroxide solution was added into ethanolic solution of **10b**. Five determinations gave values between 8210 and 8450 $M^{-1}$ cm$^{-1}$, with an average of 8300 $M^{-1}$ cm$^{-1}$.

**Product Identification.**—The uv spectrum of a solution that initially contained $9.3 \times 10^{-5}$ *M* **10b** in 95% ethanol containing $2 \times 10^{-3}$ sodium hydroxide showed, after complete disappearance of the absorbance at 373.5 mμ, a band with uv max (95% $C_2H_5OH$) 229 mμ (ε 17,500) and 282 (3320). Under the same condition the spectrum of authentic 2-phenyl-3-oxo-4-benzyl-5-methyl-6-(2-benzoyloxy)ethyl-2,3-dihydro-4H-1,4-thiazine (**8**) had uv max (95% $C_2H_5OH$) 229 mμ (ε 18,000) and 282 (3410).

**Registry No.**—**10a**, 17511-94-3; **10b**, 17511-95-4; **10c**, 17511-96-5; **10d**, 17511-97-6; **14**, 17528-36-8; **16**, 17528-37-9; **17**, 17511-98-7; **18**, 17528-38-0; **20**, 17511-99-8; **21** HCl, 17512-00-4; **22**, 17528-39-1; **23**, 17512-01-5; **24**, 17512-02-6.

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# Synthesis and Determination of the Absolute Configurations of the Enantiomeric 1,2-Epoxy-1-phenylcyclohexanes

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The enantiomeric forms of 1,2-epoxy-1-phenylcyclohexane have been prepared through a sequence involving conversion of the racemic epoxide into a mixture of 1-phenyl- and 2-phenyl-*trans*-2-dimethylaminocyclohexanols, separation and resolution of this mixture with tartaric and dibenzoyltartaric acids, and reconversion of the resolved amino alcohols into the epoxide. The absolute configurations and optical purities of the (+)-epoxide and of several other phenylcyclohexane derivatives have been determined through a series of stereospecific reactions leading to (+)-2-phenyladipic acid; application of the partial resolution method of Horeau to two of the intermediates has provided further confirmation for the stereochemical assignments.

The optically active forms of 1,2-epoxy-1-phenylcyclohexane (**2**) were needed for an extention of previous work on the stereochemistry of the ring opening of aryl-substituted cyclohexene oxides.[1-3] Since no practical method could be seen for a direct resolution of the racemic epoxide, a preparation involving cyclization of an appropriate optically active precursor appeared as the most promising approach. Racemic **2** was therefore treated with aqueous dimethylamine under pressure; this reaction had been repeatedly reported to give exclusively the amino alcohol **3**,[4-6] but it was found that the product actually consisted of a mixture of the two *trans* compounds **1** and **3**, in a ratio of about 1:2, and of some of the *cis* glycol **13**. The latter product evidently derives from the hydrolysis of **2**, which is known to proceed exclusively by *cis* opening of the ring in the absence of acids.[7]

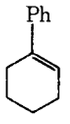
The necessity of separating the two amino alcohols **1** and **3** prior to their resolution introduced an unforeseen complication in the planned route to the optically active epoxide; luckily enough, however, it was found that the separation of isomers and the resolution could be easily carried out in one sequence, since the (+)-tartrate of (−)-**3** crystallized out in fairly good purity on treatment of the crude mixture of bases with (+)-tartaric acid. A subsequent treatment of the bases recovered from the mother liquor with (−)-dibenzoyltartaric acid gave the corresponding salt of (+)-**1**. The separation–resolution could be completed by further treatments with (−)-tartaric acid and (+)-dibenzoyltartaric acid, which led to the isolation of (+)-**3** and (−)-**1**. About 70% of the initial mixture was thus recovered in the form of bases of high optical purity.

The structures of the isomeric amino alcohols **1** and **3** were assigned on the basis of the fact that (+)-**1** was easily oxidized with Jones reagent to the ketone (−)-**4**, while (+)-**3** was recovered unchanged from a similar treatment.

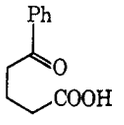
The amino alcohols **1** and **3** were reconverted into the epoxide **2** through the corresponding quaternary hydroxides. Both (−)-**1** and (+)-**3** gave the dextrorotatory epoxide **2**; (+)-**1** and (−)-**3**, the levorotatory enantiomer. All four products had specific rotations of at least ±117°, the highest value observed being +121.2° (in benzene). The close coincidence of the four values indicates that 121.2° probably corresponds very nearly to optical purity. This was confirmed

(1) G. Berti, F. Bottari, B. Macchia, and F. Macchia, *Tetrahedron*, **21**, 3277 (1965).
(2) G. Berti, F. Bottari, B. Macchia, and F. Macchia, *ibid.*, **22**, 189 (1966).
(3) G. Berti, B. Macchia, and F. Macchia, *ibid.*, **24**, 1755 (1968).
(4) J. Levy and J. Sfiras, *Bull. Soc. Chim. Fr.*, **49**, 1837 (1931).
(5) A. M. Mandrou, P. Potin, and R. Wylde-Lachazette, *ibid.*, 1546 (1962).
(6) N. B. Chapman and D. J. Triggle, *J. Chem. Soc.*, 4835 (1963).
(7) C. L. Stevens, H. T. Hanson, and K. G. Taylor, *J. Amer. Chem. Soc.*, **88**, 2769 (1966).

by a sequence leading from (+)-**2** to (+)-2-phenyladipic acid (**10**). Reaction of (+)-**2** with potassium hydroxide in dimethyl sulfoxide–water gave the *trans* glycol (+)-**5**; it had been shown before with the racemic epoxide that this reaction yields exclusively the *trans* isomer.[8] Treatment of (+)-**5** with hydrogen chloride in chloroform led to the *trans* chlorohydrin (+)-**6**, which was reduced catalytically to (+)-*cis*-2-phenylcyclohexanol (**8**); the latter two reactions had been found to proceed with retention of configuration,[2] when applied to the racemic compounds. (+)-**8** was converted through the methylxanthate (+)-**7** into (+)-3-phenylcyclohexene (**9**), a reaction which was known to yield this olefin contaminated by less than 4% 1 isomer (**11**);[9,10] this was confirmed by glpc, which showed that in the product of the pyrolysis of (+)-**7** the ratio of **9** to **11** was 98:2. (+)-**9** was converted through oxidation with osmium tetroxide, followed by cleavage with chromium trioxide, into (+)-2-phenyladipic acid (**10**);[11] some 4-benzoylbutyric acid (**12**) was also formed. Since (+)-**10**



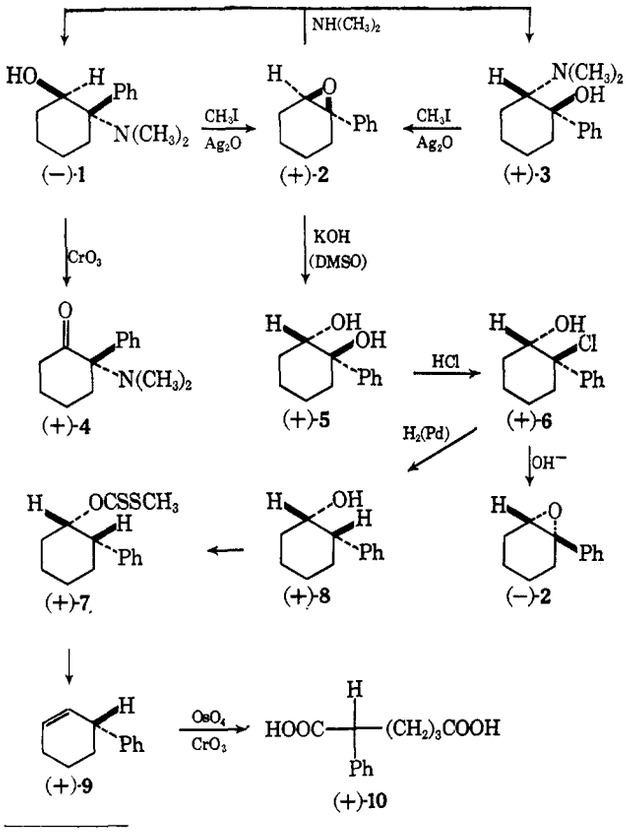

**11**




**12**

had been assigned the *S* configuration it was possible to deduce the absolute configuration of (+)-**2** and of all the compounds shown in Chart I.

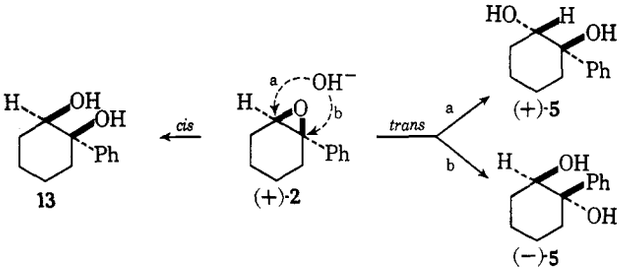
CHART I



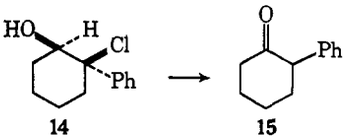

In all the reactions involved in the correlation between (+)-**2** and (+)-**10**, recrystallizations were avoided as much as possible to prevent changes in optical purity due to fractionations during purifications; crude mixtures were used for the subsequent steps, or, when necessary, purifications through absorption chromatography were employed. A recrystallization was used for the purification of the xanthate (+)-**7**; however, the purified ester was correlated directly with the precursor (+)-**8** through hydrolysis, and a corresponding correction was applied to the final calculation. Also the acid (+)-**10** had to be recrystallized to separate it from **12**, but it was possible to recover it completely, and no optical activity remained in the mother liquor.

A closer examination of the reactions in Chart I shows that, although several of them could take place with formation of more than one diastereoisomer, only the conversion of **2** into **5** (and possibly that of **9** into **10**) could lead to some racemization, since only one of two chiral atoms is involved in the other ones. As far as reaction **2** → **5** is concerned, three steric courses could be anticipated, as shown in Chart II;

CHART II




one, involving a *cis* opening of the oxirane ring to give the glycol **13**, would be rather unlikely for the alkaline hydrolysis of an epoxide and was ruled out by gas chromatographic analysis of the product. On the other hand, the *trans* opening could take place by attack either on C-2 (path) or C-1 (path b), leading, respectively, to (+)-**5** or (−)-**5**; if both modes of attack are operative some racemization must take place. This point was clarified by reconversion of the crude glycol into the epoxide **2**, through transformation into the chlorohydrin **6** and treatment of the latter with base. The displacement **5** → **6** had been shown to take place exclusively on the benzylic hydroxyl group and essentially in a *cis* stereospecific way;[2] however, even if some of the *cis* chlorohydrin (**14**) were formed, it would not interfere with the stereochemical correlation, as this compound would not give any epoxide in the treatment with base, the ketone **15** being formed instead. The epoxide obtained from




**14** **15**

(+)-**6** was found after chromatographic purification to be enantiomeric with the starting epoxide, its specific rotation having been reduced to 88.6% of the initial value. For the reasons stated above the racemization

(8) G. Berti, B. Macchia, and F. Macchia, *Tetrahedron Lett.*, 3421 (1965).
(9) E. R. Alexander and A. Mudrak, *J. Amer. Chem. Soc.*, **72**, 1810 (1950).
(10) E. L. Eliel, N. L. Allinger, S. J. Angyal, and G. A. Morrison, "Conformational Analysis," Interscience Publishers, New York, N. Y., 1965, p 103.
(11) L. Westman, *Ark. Kemi*, **12**, 167 (1958).

TABLE I

CONFIGURATIONS AND SPECIFIC ROTATIONS

| Compound | Configuration | [α]D max obsd (temp, solvent) | [α]D max calcd on the basis of ±121.2° for 2 |
|---|---|---|---|
| (−)-1 | 1*R*,2*S* | −31.9° (24°, benzene) | −31.9° |
| (+)-2 | 1*R*,2*R* | +121.2° (24°, benzene) | +121.2° |
| (+)-3 | 1*R*,2*S* | +14.9° (24°, benzene) | +14.9° |
| (−)-3 HCl | 1*R*,2*S* | −24.9° (22°, water) | −24.9° |
| (−)-4 | *S* | −65.9° (23°, benzene) | |
| (+)-5 | 1*R*,2*S* | +51.0° (27°, benzene) | +53.6° |
| (+)-6 | 1*S*,2*R* | +13.7° (24°, benzene) | +14.1° |
| (+)-7 | 1*S*,2*S* | +73.3° (29°, chloroform) | +76.6° |
| (+)-8 | 1*S*,2*S* | +97.8° (30°, benzene) | +102.2° |
| (+)-9 | *R* | +149.7° (29°, benzene) | +159.6° |
| (+)-10 | *S* | +61.0° (25°, abs ethanol) | +63.4° |

can only take place in the passage from **2** to **5**; therefore the result indicates that this reaction goes for about 94% by path a and 6% by path b, in accordance with the fact that SN2-type displacements on epoxides are more sensitive to steric factors than to the bond-weakening effects caused by aryl substituents.[3,12] In the similar reaction between **2** and dimethylamine the percentage of attack on the benzylic carbon to give the amino alcohol **1** is higher; probably, in this case, in the presence of a weaker base the transition state has more of a "borderline SN2" character.[12]

The catalytic reduction of crude (+)-**6** gave mostly (+)-*cis*-2-phenylcyclohexanol (**8**) containing only a small amount of the *trans* isomer. The latter, which could originate either from a contamination of **6** with some **14**, or from an incomplete stereospecificity of the reduction, was easily eliminated by column chromatography.

When the specific rotation found for (+)-**10** was corrected for the racemization involved in the step **2** → **5** and for the changes in optical purity occurring in some of the purifications, a value of [α]D +63.4° was calculated for the acid **10** corresponding to a starting epoxide with [α]D +121.2°; the highest one reported in the literature for the acid is [α]D +63.8°,[11] a fact which confirms that 121.2° must be very near to the specific rotation for the optically pure epoxide **2**. Scheme I gives the numerical values used in the correlation of (+)-**2** with (+)-**10**, while Table I summarizes the specific rotations that were calculated for all compounds in Chart I.

SCHEME I

CORRELATION OF (+)-2 WITH (+)-10[a]

(+)-**2** (+116.6°; 96.2%) → (+)-**5** (...; 85.2%)

↓

(+)-**8** (+87.1°; 85.2%) ← (+)-**6** (...; 85.2%) → (−)-**2** (−103.3°; 85.2%)

(+)-**8** (+92.9°; 90.9%) → (+)-**7** (+73.3°; 95.7%)[b] → (+)-**8** (+97.8°; 95.7%)

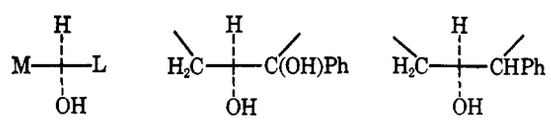
↓

(+)-**10** (+60.7°; 95.7%) ← (+)-**9** (+152.7°; 95.7%)[c]

[a] Values in parentheses indicate [α]D and optical purity, based on [α]D +121.2° for (−)-**2**. [b] Recrystallized product. [c] Corrected for the presence of 2% 1-phenylcyclohexene.

(12) R. E. Parker and N. S. Isaacs, *Chem. Rev.*, **59**, 737 (1959).

Since the absolute configuration of **10** had been determined by the method of quasiracemates,[11] which, although usually quite reliable, cannot be considered as a complete proof, we checked the configurational attributions by applying the partial resolution method of Horeau[13,14] to the alcohols (+)-**5** and (+)-**8**. In both cases the recovered 2-phenylbutyric acid was levorotatory, and the optical yield was around 50%. This is in good agreement with the assigned configurations as, according to the rules of Horeau, the recovery of levorotatory acid indicates configuration **16** for the chiral center, which would correspond to configurations **17** and **18** for C-2 of (+)-**5** and (+)-**8**. The tertiary hydroxy group of (+)-**5** is apparently not esterified even in the presence of a large excess of 2-phenylbutyric anhydride.




**16** **17** **18**

It may also be pointed out that the configurational assignments discussed above are in good agreement with those that can be deduced from the semiempirical rules of Brewster for cyclohexane derivates.[15]

## Experimental Section[16]

**Reaction of 1,2-Epoxy-1-phenylcyclohexane [(±)-2] with Dimethylamine.**—A mixture of (±)-**2**[1] (66 g, 0.38 mol) and 40% aqueous dimethylamine (250 ml, 2.2 mol) was heated at 150° for 24 hr in a magnetically stirred 1-l. autoclave. The product was extracted with three 200-ml portions of ether; the ether solution, after washing with water (200 ml) and thorough extraction with 1 *N* hydrochloric acid, left on evaporation a neutral crystalline residue (12.5 g) of slightly impure 1-phenyl-*cis*-cyclohexane-1,2-diol (**13**).[1] The acidic extract was made alkaline with 32% aqueous ammonia and extracted three times with 200 ml of ether; the ether was evaporated, and the residue was distilled; the product [54 g; bp 100–120° (0.2 mm); $n^{24}$D 1.5478] was a mixture of 1-phenyl-*trans*-2-dimethylaminocyclohexanol (**3**) and 2-phenyl-*trans*-2-dimethylaminocyclohexanol (**1**).

**Separation and Resolution of the Mixture of 1 and 3.**—A solution of the mixture of amino alcohols described above (66.1 g, 0.30 mol) in 312 ml of 95% ethanol was heated at 60–70° and treated with (+)-tartaric acid (47 g, 0.31 mol) in 312 ml of 95% ethanol. The precipitate was collected after one night. Salt A (20 g) was obtained: mp 177–179°; [α]$^{23}$D +29.2° (*c* 1.28, $H_2O$). A sample was crystallized repeatedly from ethanol to give pure (1*S*,2*R*)-1-phenyl-*trans*-2-dimethylaminocyclohexanol (+)-tartrate: needles; mp 180–183°; [α]$^{24}$D +30.1° (*c* 1.35, $H_2O$).

*Anal.* Calcd for $C_{18}H_{27}NO_7$: C, 58.52; H, 7.37. Found: C, 58.23; H, 7.39.

The mother liquor of salt A was evaporated to dryness *in vacuo;* the residue was taken up in 900 ml of water, treated with 10% aqueous sodium hydroxide (200 ml), and extracted with ether. The mixture of bases obtained on evaporation of the ether layer (54.1 g) was dissolved in 95% ethanol (300 ml) and water (55 ml), treated with a hot solution of (−)-dibenzoyltartaric acid monohydrate (96.6 g, 0.257 mol) in ethanol (330

(13) A. Horeau and H. B. Kagan, *Tetrahedron*, **20**, 2431 (1964).

(14) R. Weidmann and A. Horeau, *Bull. Soc. Chim. Fr.*, 117 (1967).

(15) J. H. Brewster, *J. Amer. Chem. Soc.*, **81**, 5483, 5493 (1959).

(16) Melting points were determined on a Kofler hot stage and are uncorrected. Ir spectra were taken with a Perkin-Elmer Infracord Model 137 or a Perkin-Elmer 237 grating spectrophotometer and uv spectra with a Beckman Model DU spectrophotometer. Gas–liquid partition chromatograms were run on a Carlo Erba Fractovap Model GV apparatus with a flame ionization detector. Optical rotations were determined with a Perkin-Elmer 141 photoelectric polarimeter. Comparisons between compounds were made on the basis of their ir spectra. Petroleum ether refers to the fraction with bp 30–50°. Magnesium sulfate was used as the drying agent, unless stated otherwise.

ml) and water (55 ml), and stored overnight. (1*S*,2*R*)-2-Phenyl-*trans*-2-dimethylaminocyclohexanol (−)-dibenzoyltartrate (salt B, 20.5 g) crystallized out. An analytical sample was obtained from ethanol–water as blades: mp 190–192°; $[\alpha]^{24}D$ −32.3° (*c* 1.0, N,N-dimethylformamide).

*Anal.* Calcd for $C_{32}H_{35}NO_9$: C, 66.54; H, 6.11. Found: C, 66.16; H, 6.24.

The free bases (44 g), recovered as described above from the mother liquor of salt B, were dissolved in ethanol (210 ml) and treated with (−)-tartaric acid (30 g) in ethanol (210 ml) to yield practically pure (1*R*,2*S*)-1-phenyl-*trans*-2-dimethylaminocyclohexanol (−)-tartrate (salt C, 32.8 g): mp 180–181°; $[\alpha]^{24}D$ −30.2° (*c* 0.52, $H_2O$).

*Anal.* Calcd for $C_{18}H_{27}NO_7$: C, 58.52; H, 7.37. Found: C, 58.34; H, 7.52.

The free bases (22.6 g), recovered from the mother liquor of salt C, dissolved in ethanol (200 ml) and water (33 ml), and treated with (+)-dibenzoyltartaric acid monohydrate (38.0 g) in ethanol (200 ml) and water (33 ml), yielded (1*R*,2*S*)-2-phenyl-*trans*-2-dimethylaminocyclohexanol (+)-dibenzoyltartrate (salt D, 24.9 g, mp 186–188°), which was crystallized from ethanol–water to give blades: mp 192–193°; $[\alpha]^{25}D$ +26.8° (*c* 0.56, N,N-dimethylformamide).

*Anal.* Calcd for $C_{32}H_{35}NO_9$: C, 66.54; H, 6.11. Found: C, 66.51; H, 6.11.

(1*S*,2*R*)-(−)-**1-Phenyl-*trans*-2-dimethylaminocyclohexanol** [(−)-**3**].—A solution of salt A (20.0 g) in water (200 ml) was treated with 10% aqueous NaOH (50 ml) and extracted with ether. The washed ($H_2O$) and dried ether extract gave after evaporation an oily residue of (−)-**3** (11.6 g, 18% yield, calculated on the starting mixture of amino alcohols), $[\alpha]^{23}D$ −14.9° (*c* 1.29, $C_6H_6$). The hydrochloride, prepared with hydrogen chloride in ether, was crystallized from ethanol–ether: mp 160–161° [(±)-**3** HCl, lit.[7] mp 204–206°]; $[\alpha]^{22}D$ +24.6° (*c* 0.33, $H_2O$).

*Anal.* Calcd for $C_{14}H_{22}ClNO \cdot {}^1/_2H_2O$: C, 63.50; H, 8.76; N, 5.29. Found: C, 63.54; H, 8.92; N, 4.93.

(1*R*,2*S*)-(+)-**1-Phenyl-*trans*-2-dimethylaminocyclohexanol** [(+)-**3**].—The base obtained from salt C (19.0 g, 28% yield) was an oil, $[\alpha]^{24}D$ +14.9° (*c* 1.06, $C_6H_6$). The corresponding hydrochloride was crystallized from ethanol–ether: mp 159–160°; $[\alpha]^{22}D$ −24.9° (*c* 0.56, $H_2O$).

*Anal.* Calcd for $C_{14}H_{22}ClNO \cdot {}^1/_2H_2O$: C, 63.50; H, 8.76; N, 5.29. Found: C, 63.42; H, 8.78; N, 5.16.

(1*S*,2*R*)-(+)-**2-Phenyl-*trans*-2-dimethylaminocyclohexanol** [(+)-**1**].—The base obtained as above from salt B (7.7 g, 12% yield), $[\alpha]^{23}D$ +26.3° (*c* 1.10, $C_6H_6$), was crystallized repeatedly from petroleum ether to a constant specific rotation to give a product: mp 75–76.5° [(±)-**1**, lit.[17] mp 78–80°]; $[\alpha]^{25}D$ +31.3° (*c* 0.97, $C_6H_6$).

*Anal.* Calcd for $C_{14}H_{21}NO$: C, 76.66; H, 9.65. Found: C, 76.79; H, 9.57.

(1*R*,2*S*)-(−)-**2-Phenyl-*trans*-2-dimethylaminocyclohexanol** [(−)-**1**].—The base obtained from salt D (8.4 g, 13% yield) had $[\alpha]^{24}D$ −30.7° (*c* 1.25, $C_6H_6$). Repeated crystallizations from petroleum ether gave a sample: mp 75.5–77°; $[\alpha]^{24}D$ −31.9° (*c* 1.59, $C_6H_6$).

*Anal.* Calcd for $C_{14}H_{21}NO$: C, 76.66; H, 9.65. Found: C, 76.80; H, 9.96.

(*S*)-(−)-**2-Dimethylamino-2-phenylcyclohexanone** [(−)-**4**].—A solution of (+)-**1** (0.174 g), $[\alpha]^{25}D$ +31.3° in acetone (5 ml), was oxidized with Jones reagent[18] (0.20 ml), diluted with water after 1 min, made alkaline with aqueous ammonia, and extracted with ether. Evaporation of the ether left an oily residue (0.140 g), ir (neat) 1710 $cm^{-1}$ (C=O), which was converted into the picrate of (−)-**4**. The salt was crystallized from ethanol: mp 187–188° [(±)-**4** picrate, lit.[17] mp 199–200°].

*Anal.* Calcd for $C_{20}H_{22}O_8N_4 \cdot H_2O$: C, 51.72; H, 5.21; N, 12.06. Found: C, 51.70; H, 5.26; N, 12.05.

A solution of the purified picrate (70 mg) in ether (20 ml) was washed with five 5-ml portions of 10% aqueous sodium hydroxide, then with water, dried, and evaporated; the residue of (−)-**4** (26 mg) had $[\alpha]^{23}D$ −65.9° (*c* 0.26, $C_6H_6$).

(+)-**3** was recovered unchanged from a similar treatment.

(1*S*,2*S*)-(−)-**1,2-Epoxy-1-phenylcyclohexane** [(−)-**2**]. **A.**—A solution of (−)-**3** (4.0 g, $[\alpha]^{23}D$ −14.9°) and methyl iodide (22.8 g) in absolute methanol (40 ml) was refluxed 1 hr, then evaporated to dryness *in vacuo* to give the methiodide of (−)-**3** (6.95 g). An analytical sample was obtained by crystallization from methanol–ether: mp 206–207° [(±)-**3** methiodide, lit.[7] mp 212–214°]; $[\alpha]^{20}D$ +11.1° (*c* 0.28, $C_2H_5OH$).

*Anal.* Calcd for $C_{15}H_{24}INO$: C, 49.86; H, 6.70; N, 3.88. Found: C, 49.80; H, 6.80; N, 4.06.

The crude methiodide (6.85 g) in water (200 ml) was shaken for 5 hr with silver oxide freshly prepared from 15.0 g of silver nitrate. The mixture was filtered; the precipitate was washed with ether; the ether was evaporated; and the residue was added to the aqueous solution, which was steam distilled. The distillate was extracted with ether, and the ether evaporated to give (−)-**2** (2.43 g): $[\alpha]^{24}D$ −119.6° (*c* 1.85, $C_6H_6$); $[\alpha]^{35}D$ −75.5° (*c* 0.70, $CHCl_3$); $[\alpha]^{35}D$ −119.0° (neat).

**B.**—(+)-**1** (6.94 g, $[\alpha]^{23}D$ +30.9°) gave, when treated as described in A, 12.8 g of the methiodide of (+)-**1**: mp 137–139° (from acetone) [(±)-methiodide, lit.[17] mp 144–146°]; $[\alpha]^{25}D$ +31.4° (*c* 0.87, $C_2H_5OH$).

*Anal.* Calcd for $C_{15}H_{24}INO$: C, 49.86; H, 6.70. Found: C, 49.55; H, 6.38.

The methiodide, treated as described in A, gave 4.50 g of crude (−)-**2**, $[\alpha]^{25}D$ −108.0° (*c* 1.08, $C_6H_6$), which was distilled over a little potassium hydroxide[1] to give the pure product (3.9 g): bp 121° (1.5 mm); $n^{26}D$ 1.5419 [lit.[1] bp 118° (0.5 mm); $n^{19}D$ 1.5430]; $[\alpha]^{26}D$ −117.3° (*c* 1.28, $C_6H_6$).

(1*R*,2*R*)-(+)-**1,2-Epoxy-1-phenylcyclohexane** [(+)-**2**].—A method recently described by Stevens, *et al.*,[7] for the preparation of (±)-**2** was used.

**A.**—A solution of (+)-**3** (17.7 g, $[\alpha]^{24}D$ +14.9°) in methanol (130 ml) was converted by 1-hr reflux with methyl iodide (36 g) into the methiodide: mp 204–205° (after crystallization from methanol–ether); $[\alpha]^{22}D$ −11.5° (*c* 0.36, $C_2H_5OH$).

*Anal.* Calcd for $C_{15}H_{24}INO$: C, 49.86; H, 6.70; N, 3.88. Found: C, 49.52; H, 6.96; N, 3.57.

The crude methiodide was dissolved in ethanol (1800 ml) and treated with a suspension of silver oxide, prepared from silver nitrate (21.3 g) and sodium hydroxide (11.2 g) in water (550 ml). The mixture was shaken for 2 hr and filtered. The filtrate and the residue were extracted with petroleum ether; the combined and dried ($K_2CO_3$) extracts were evaporated to give (+)-**2** (11.7 g), $[\alpha]^{25}D$ +116.0° (*c* 0.84, $C_6H_6$). A part of this product (0.2 g) was purified by chromatography through a 15 × 20 cm column of neutral alumina (grade II). The first 100-ml eluate (hexane) yielded pure (+)-**2** (0.090 g), $[\alpha]^{24}D$ +121.2° (*c* 0.78, $C_6H_6$). The low recovery was due to partial decomposition of the epoxide during the chromatography to products which were, however, retained by the column.

**B.**—(−)-**1** (0.309 g, $[\alpha]^{26}D$ −31.6°), when treated in the same manner, gave, after chromatography of the final product, (+)-**2** (0.062 g), $[\alpha]^{25}D$ +119.9° (*c* 0.60, $C_6H_6$).

(1*R*,2*S*)-(+)-**1-Phenyl-*trans*-cyclohexane-1,2-diol** [(+)-**5**].—A solution of (+)-**2** (5 g, $[\alpha]^{25}D$ +116.0°) in dimethyl sulfoxide (100 ml) and 10 *N* aqueous potassium hydroxide (18 ml) was heated for 70 hr at 100°.[8] The mixture was evaporated to dryness *in vacuo*, and the residue extracted with 200 ml of ether. The extract was washed with 100 ml of water and evaporated to give 4.6 g of crude (+)-**5**, $[\alpha]^{23}D$ +40.8° (*c* 0.49, $C_6H_6$). Repeated crystallizations from chloroform–hexane gave a sample: mp 79–80° [(±)-**5**, lit.[1] mp 98.5–100°]; $[\alpha]^{27}D$ +51.0° (*c* 0.37, $C_6H_6$).

A sample of the crude (+)-**5** (0.5 g) was purified by chromatography through a 1.5 × 40 cm column of neutral alumina (grade II). Elution with 7:3 benzene–ether gave chemically pure (+)-**5**, $[\alpha]^{24}D$ +45.7° (*c* 0.54, $C_6H_6$).

(1*S*,2*R*)-(+)-**2-Phenyl-*trans*-2-chlorocyclohexanol** [(+)-**6**].—(+)-**5** (0.577 g, $[\alpha]^{28}D$ +49.3°) was treated with a 0.1 *N* solution of hydrogen chloride in chloroform (130 ml).[2] After 3 hr the solution was washed with saturated $NaHCO_3$ and water and was evaporated *in vacuo*. The residue was crystallized repeatedly from petroleum ether to give (+)-**6** (0.360 g): mp 44.5–45° [(±)-**6**, lit.[2] mp 89–91°]; $[\alpha]^{24}D$ +13.7° (*c* 0.58, $C_6H_6$).

**Conversion of (+)-6 into (−)-2.**—A solution of (+)-**6** (0.496 g, $[\alpha]^{25}D$ +13.7°) in methanol (20 ml) was titrated with 0.1 *N* aqueous sodium hydroxide (phenolphthalein). After 15 min the reaction was complete, the theoretical amount of base having been consumed. Dilution with water, extraction with chloroform, and evaporation of the dried extract *in vacuo* gave an oily residue (0.36 g), the ir spectrum of which was identical with that of **2**. It was passed through a 1.5 × 20 cm column of neutral alumina

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(grade II); the first 200 ml of eluate (hexane) yielded pure (−)-**2**, $[\alpha]^{25}D$ −117.5° (*c* 1.00, $C_6H_6$).

(1*S*,2*S*)-(+)-*cis*-**2-Phenylcyclohexanol** [(+)-**8**].—A preliminary test was made on (±)-**6** (0.23 g) which was hydrogenated in ethanol (40 ml) over 5% palladium on calcium carbonate (0.2 g) at room temperature and pressure. After 1 hr the catalyst was filtered off; the solution was evaporated to dryness *in vacuo;* and the residue crystallized from petroleum ether to give (±)-**8**, mp 41–42° (lit.[19] mp 41–42°). The same reaction was repeated with (+)-**6**, $[\alpha]^{24}D$ +12.7°, and the crude product (1.32 g), $[\alpha]^{24}D$ +78.9° (*c* 0.59, $C_6H_6$), was dissolved in hexane and chromatographed through a 1.5 × 26 cm column of neutral alumina (grade II). Elution with hexane (3600 ml) and 7:3 hexane–benzene (1200 ml) gave (+)-**8** (0.770 g): liquid; $[\alpha]^{20}D$ +92.9° (*c* 1.18, $C_6H_6$). Further elution with hexane–benzene (1500 ml) and with benzene (700 ml) yielded *trans*-2-phenylcyclohexanol (36 mg): $[\alpha]^{31}D$ +47.6° (*c* 1.56, $C_6H_6$). A final elution with ether gave (+)-**5** (140 mg).

**Direct Correlation of (+)-8 with (+)-2.**—The reactions described above were repeated without purification of the intermediates, in the following way. (+)-**2** (0.504 g, $[\alpha]^{25}D$ +116.6°, purified through chromatography) was converted into crude (+)-**5** {0.449 g, $[\alpha]^{22}D$ +43.7° (*c* 1.14, $C_6H_6$)}, 0.437 g of which was treated with hydrogen chloride in chloroform, as described above, to give crude (+)-**6** (0.405 g). A part of this (0.086 g) was reconverted with sodium hydroxide into the epoxide, which was purified through chromatography, $[\alpha]^{25}D$ −103.3° (*c* 0.694, $C_6H_6$). The rest of the crude (+)-**6** (0.32 g) was reduced catalytically, as above, to a crude product, which was subjected to chromatography to give pure (+)-**8**: liquid; $[\alpha]^{27}D$ +87.1° (*c* 0.288, $C_6H_6$). The purity was checked through tlc ($SiO_2$ F 254 Merck, benzene), a single spot being observed; the *trans* isomer of **8** can easily be detected under these conditions, as it has a smaller $R_f$ value.

(1*S*,2*S*)-(+)-*cis*-**2-Phenylcyclohexanol Methylxanthate** [(+)-**7**].—The method of Alexander and Mudrak[20] for the preparation of the corresponding racemic compound was followed. A solution of (+)-**8**, $[\alpha]^{29}D$ +92.9° (0.535 g, 3.0 mmol), in anhydrous ether (5 ml) was shaken for 70 hr at room temperature with sodium (0.100 g, 4.35 mg-atom) cut in thin slices; carbon disulfide (0.72 g, 9.1 mmol) was slowly added; excess sodium was eliminated mechanically; stirring was continued for 30 min; methyl iodide (2.0 g, 14.4 mmol) was added; and the mixture was stirred for 46 hr, more methyl iodide (0.25 g) being added after 24 and 44 hr. The mixture was filtered and evaporated *in vacuo*, and the residue (0.760 g) was chromatographed through a 1.4 × 22 cm column of neutral alumina (grade II). Hexane (300 ml) eluted (+)-**7** (0.66 g), $[\alpha]^{31}D$ +67.9° (*c* 1.82, $CHCl_3$), which was crystallized from ethanol at −10° to give the pure product (0.49 g): mp 57.5–58.5° [(±)-**7**, lit.[20] mp 49–50°]; $[\alpha]^{29}D$ +73.3° (*c* 0.44, $CHCl_3$).

*Anal.* Calcd for $C_{14}H_{18}OS_2$: C, 63.11; H, 6.81. Found: C, 62.81; H, 6.77.

A solution of the pure (+)-**7** (81 mg) was refluxed for 100 min with 3% potassium hydroxide in ethanol (3 ml), then diluted with water (10 ml), and extracted with hexane (30 ml). Evaporation of the extract and chromatography of the residue through alumina gave (+)-**8** (16 mg), $[\alpha]^{30}D$ +97.8° (*c* 1.07, $C_6H_6$).

(*R*)-(+)-**3-Phenylcyclohexene** [(+)-**9**].—(+)-**7** (0.400 g, $[\alpha]^{29}D$ +73.3°) was heated for 40 min at 210° and 5 min at 240°. The residue was extracted with hexane and chromatographed through neutral alumina (1 × 24 cm, grade I). The first 80 ml of eluate gave (+)-**9** as a colorless oil (0.087 g): $[\alpha]^{29}D$ +149.7° (*c* 0.53, $C_6H_6$); uv max (95% $C_2H_5OH$) 248 and 252.5 mμ (ε 635 and 653) [(±)-**9**, lit.[21] uv max 253 mμ (ε 653); 1-phenylcyclohexene, uv max 247 mμ (ε 12,940)]; the ir bands reported in the literature[22] for (±)-**9** were all present, those reported for 1-phenylcyclohexene absent or barely visible. Glpc analysis (2-m column, i.d. 3 mm, of 1% neopentyl glycol succinate on silanized Chromosorb W 80–100 mesh, 100°) indicated that the product consisted of 98% **9** and 2% 1-phenylcyclohexene (**11**) (relative retention times 1:1.97). Preliminary tests had shown that the passage through alumina does not cause any conversion of **9** into **11**.

(*S*)-(+)-**2-Phenyladipic Acid** [(+)-**10**].—A solution of (+)-**9** (70 mg, 0.44 mmol), $[\alpha]^{29}D$ +149.7°, in ether (3 ml) and pyridine (0.26 ml) was treated with osmium tetroxide (120 mg, 0.46 mmol) in ether (3 ml). After 6 days the brown precipitate was collected, dissolved in methylene chloride (10 ml), treated with sodium hydroxide (0.20 g) and mannitol (0.50 g ) in water (8 ml), and shaken until the color disappeared. Evaporation of the organic layer gave a mixture of diastereoisomeric 3-phenyl-*cis*-cyclohexane-1,2-diols (0.085 g), mp 86–88°, which was dissolved in acetone (5 ml) and oxidized with 0.49 ml of Jones reagent.[18] After 5 min saturated sodium chloride was added, and the solution was extracted with ether. The ether layer was washed with saturated sodium chloride, dried, and evaporated to give a solid residue (75 mg). Crystallization from benzene gave (+)-**10**: needles (30 mg); mp 152–153.5°; $[\alpha]^{25}D$ +61.0° (*c* 0.39, absolute $C_2H_5OH$) (lit.[11] mp 153–155°, $[\alpha]^{25}D$ +63.8°). From the mother liquor, after treatment with charcoal and dilution with petroleum ether, another 4.5 mg of (+)-**10**, $[\alpha]^{25}D$ +59.0°, was obtained. Complete evaporation of the mother liquor gave an optically inactive product which was crystallized from water to give 4-benzoylbutyric acid (**12**), mp 118–120° (lit.[23] mp 119–123.5°); it was identical with an authentic sample of **12**, prepared by permanganate oxidation of 1-phenylcyclopentene.

**Determinations of Absolute Configurations through Partial Resolution. A.**—According to the method of Horeau, a solution of 2-phenylbutyric anhydride (0.506 g, 1.63 mmol) in pyridine (5 ml) was added to (+)-**5** (74.6 mg, 0.39 mmol, $[\alpha]^{26}D$ +49.6°). After 18 hr at room temperature 2 drops of water was added; the mixture was heated 30 min on a steam bath and after addition of benzene (6 ml) titrated with 0.1 *N* sodium hydroxide (phenolphthalein), 30.2 ml being consumed; the esterification yield was 62%. The water layer was washed with benzene, acidified with hydrochloric acid, and extracted with three 15-ml portions of benzene. The benzene extract was evaporated, and the residue brought to a volume of 5 ml with benzene: $[\alpha]^{28}D$ −0.377° (1 dm); optical yield 50%.

**B.**—The same treatment was repeated on the alcohol (+)-**8** (32.8 mg, $[\alpha]^{23}D$ +94.6°) with 109 mg of 2-phenylbutyric anhydride in 1 ml of pyridine [0.1 *N* sodium hydroxide (6.23 ml); esterification yield 45%; recovered 2-phenylbutyric acid (in 2.0 ml of benzene), $[\alpha]^{26}D$ −0.304° (1 dm); optical yield 47%].

**Registry No.**—(+)-**1**, 17539-99-0; (+)-**1** methiodide, 17540-00-0; (+)-**1** (−)-dibenzoyltartrate, 17540-01-1; (−)-**1**, 17540-02-2; (−)-**1** (+)-dibenzoyltartrate, 17540-03-3; (+)-**2**, 17540-04-4; (−)-**2**, 5775-23-5; (+)-**3**, 17540-06-6; (+)-**3** HCl, 10276-01-4; (+)-**3** methiodide, 17540-21-5; (+)-**3** (−)-tartrate, 17540-08-8; (−)-**3**, 17540-09-9; (−)-**3** HCl, 17540-10-2; (−)-**3** methiodide, 10276-02-5; (−)-**3** (+)-tartrate, 17540-12-4; (−)-**4**, 17540-13-5; (−)-**4** picrate, 17540-14-6; (+)-**5**, 17540-15-7; (+)-**6**, 5775-43-9; (+)-**7**, 17540-17-9; (+)-**8**, 17540-18-0; (+)-**9**, 17540-19-1; (+)-**10**, 17540-20-4.

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