Anal. Calcd for $C_{15}H_{22}O_4$: C, 67.65; H, 8.33; O, 24.03. Found: C, 67.21; H, 8.37; O, 24.46.

B.—Reduction of 0.279 g of **1a** with 0.265 g of $NaBH_4$ in the manner described in the previous paragraph gave a noncrystalline product (**3**) which was purified by preparative tlc: $[\alpha]^{24}D$ −41.4° (*c* 5.8); ir bands at 3580, 3480, 1760, and 1600 cm^{-1}.

Anal. Calcd for $C_{15}H_{24}O_4$: C, 67.14; H, 9.01; O, 23.85. Found: C, 67.09; H, 9.18; O, 23.48.

Dehydroparthemollin (4).—A solution of 0.243 g of **1a** in 25 ml of dry chloroform was stirred with 2.4 g of activated manganese dioxide at room temperature for 4 days and filtered, the precipitate being washed thoroughly with chloroform. The combined filtrate and washings were evaporated at reduced pressure and the residual gum purified by preparative tlc. This gave 0.13 g of **4** and 0.1 g of recovered starting material. The product was recrystallized from ethyl acetate–petroleum ether: mp 95–97°; ir 1760, 1660, and 1600 cm^{-1}; uv λ_{max} 294 and 210 nm (ϵ 16,200 and 17,550).

Anal. Calcd for $C_{15}H_{18}O_4$: C, 68.69; H, 6.92; O, 24.40. Found: C, 68.22; H, 7.05; O, 24.84.

Anhydroparthemollin (6).—A solution of 0.15 g of **1b** in benzene was chromatographed over a column of basic alumina. The eluate was evaporated and recrystallized from ethyl acetate–petroleum ether to give 0.065 g of **6**: mp 78–80°; ir 1760, 1708, 1665, and 1595 cm^{-1}; uv λ_{max} 277 and 205 nm (ϵ 17,500 and 15,500). The material polymerized on standing.

Anal. Calcd for $C_{15}H_{18}O_3$: C, 73.15; H, 7.37; O, 19.49. Found: C, 73.05; H, 7.21; O, 19.32.

Oxidation of Parthemollin to α-Methylglutaric Acid.—A solution of 1.0 g of **1a** in 100 ml of ethyl acetate was ozonized at 0° for 1 hr. After addition of 20 ml of water the mixture was warmed on the water bath for 0.5 hr. The solvents were removed at reduced pressure. The residue was taken up in 100 ml of 5% sulfuric acid and a solution of 5 g of $KMnO_4$ in 120 ml of water was added dropwise in 4 hr. The precipitate of manganese dioxide was reduced with sulfur dioxide solution in water. The clear solution was concentrated to 20 ml of at reduced pressure and extracted with ether. The washed and dried ether extract was evaporated and the residual gum was chromatographed over acid-washed alumina. Elution with chloroform–methanol (9:1) gave 0.35 g of gum which was dissolved in acetone and mixed with cyclohexylamine. The precipitated cyclohexylamine salt was recrystallized from ethanol–acetone and then melted at 168–171°. Decomposition of the salt with dilute hydrochloric acid, extraction with ether, washing, drying, and evaporation of the ether extract yielded 0.21 g of (*S*)-(+)-α-methylglutaric acid which was recrystallized from ethyl acetate–petroleum ether, mp 80–82°, $[\alpha]^{24}D$ +21.6° (ethanol, *c* 5.3). The melting point was undepressed on admixture of an authentic sample of mp 78–80°, $[\alpha]^{24}D$ +18° (*c* 1.24) and their ir spectra (Nujol) were superimposable.

Anal. Calcd for $C_6H_{10}O_4$: C, 49.31; H, 6.90. Found: C, 49.25; H, 6.90.

Preparation of 9, 10, and 11.—A solution of 0.310 g of **1a** and 0.8 ml of ethanedithiol in 10, ml of ether was mixed with 1.2 ml of boron trifluoride etherate and allowed to stand at room temperature. After 15 min concentrated aqueous potassium carbonate solution was added and the product was extracted with ether. Evaporation of the washed and dried extract gave crystalline **9**: mp 128–131°; $[\alpha]^{25}D$ −61.7° (*c* 2.02); ir 3410, 1750, and 1653 cm^{-1}.

A solution of 0.15 g of **9** in 10 ml of methanol–dioxane (1:1) were reduced with $NaBH_4$ as described in the preparation of **3**. The noncrystalline product **10** was purified by preparative tlc: $[\alpha]^{24}D$ −34.0° (*c* 5.62); ir 3420 and 1762 cm^{-1}.

A solution of 0.10 g of **10** in 10 ml of tetrahydrofuran was added dropwise with stirring to a slurry of 0.240 g of $LiAlH_4$ at 0°. Stirring was continued overnight at room temperature. Excess reducing agent was decomposed by addition of ethyl acetate. The mixture was acidified and the solvents were removed. The residue was taken up in chloroform. The washed and dried extract was evaporated and the noncrystalline product **11** was purified by preparative tlc, wt 30 mg, $[\alpha]^{24}D$ −13.7° (*c* 2.9).

Reaction of 1a with Phenylbutyric Anhydride.—The method of ref 22 was employed, using 211 mg (6.8×10^{-4} mol) of α-phenylbutyric anhydride and 61 mg (2.27×10^{-4} mol) of **1a**. The recovered α-phenylbutyric acid weighed 133 mg (constant weight after drying *in vacuo*, pure on tlc), $\alpha^{24}_{546.1}$ −0.064° (5 ml of benzene, 4-ml tube, measured on a Bendix Type 143A automatic polarimeter), $[\alpha]^{24}_{546.1}$ −5.97°. This corresponded to an optical yield of 25–30% ($[\alpha]D$ of α-phenylbutyric acid is ±96.5°, but a specimen of optically pure acid for determination of the rotation at the $Hg_{546.1}$ line was not available).

Registry No.—**1a**, 23264-32-6; **1b**, 23264-33-7; **2**, 23264-34-8; **3**, 23263-98-1; **4**, 23263-99-2; **6**, 23282-28-2; **7**, 1115-82-8; **8**, 23264-01-9; **9**, 23264-02-0; **10**, 23264-03-1; **11**, 23264-04-2.

The Absolute Configuration of α-*t*-Butylphenylacetic Acid and Some Derivatives[1]

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The absolute configurations of α-isopropylphenylacetic acid and α-*t*-butylphenylacetic acid have been established as *R*-(−) by relating them chemically to (*S*)-(+)-hydratropic acid through (*R*)-(−)-2-methyl-3-phenylbutane (**2**) and (*S*)-(−)-2,2-dimethyl-3-cyclohexylbutane (**8**). (+)-*t*-Butylphenylcarbinol (**16**) and (+)-β-*t*-butyl-β-phenylpropionic acid (**13**) have been related to α-*t*-butylphenylacetic acid (**9**) and shown to have the *R* configuration. These experiments resolve the uncertainties concerning the configurations of these compounds. The method of configurational correlation of these and related compounds is outlined in formulas **1–16**.

There has been considerable controversy concerning the absolute configuration of α-isopropylphenylacetic acid[2–4] (**3**). Červinka and Hub[2] reported a method for correlating configurations of α-substituted phenylacetic acids, which involved the reaction of an excess of the racemic acid with the chiral amine (*S*)-(+)-1-phenyl-2-methylaminopropane, and measuring the optical rotation of the recovered, unreacted acid. They concluded that the α-alkylphenylacetic acids which they tested[5] had the absolute *S*-(+) configuration with the exception of α-isopropylphenylacetic acid which had the *S*-(−) configuration. These experiments were repeated by Halpern and Westley[3] who failed to confirm this latter exception and concluded that all these α-substituted phenylacetic acids had the *S*-(+) configuration including the α-isopropyl derivative. We

(1) We acknowledge with thanks support of these studies by the National Science Foundation, Grant NSF GP 9452.

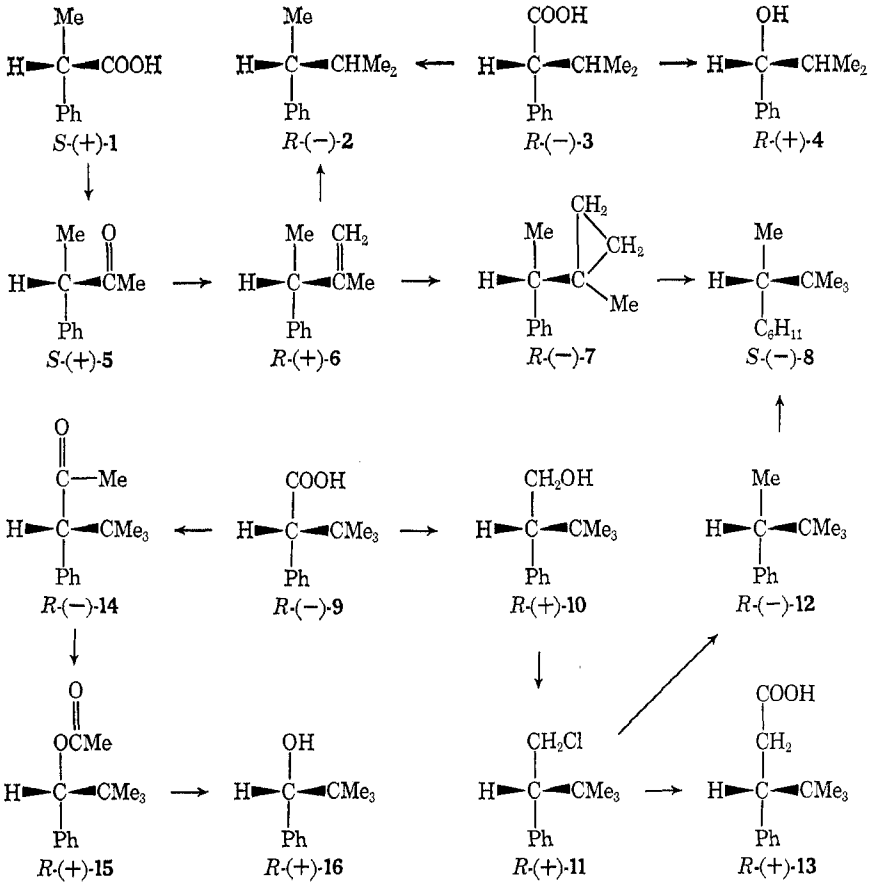
(2) (a) O. Červinka and L. Hub, *Chem. Commun.*, 761 (1966); (b) *Collect. Czech. Chem. Commun.*, **32**, 2295 (1967).

(3) B. Halpern and J. Westley, *Chem. Commun.*, 237 (1967).

(4) C. Aaron, D. Dull, J. L. Schmiegel, D. Jaeger, Y. Ohashi, and H. S. Mosher, *J. Org. Chem.*, **32**, 2797 (1967).

(5) The alkyl groups included methyl, ethyl, *n*-propyl, *n*-butyl, *n*-amyl, *n*-hexyl, iso-propyl, iso-butyl, benzyl, and allyl.

SCHEME I



also had concluded,[4] on the basis of the optical rotatory shifts of a series of acid derivatives according to the Freudenberg method,[6] and on the basis of the optical rotatory dispersion (ORD) curves of the thionamide derivatives[7] of these acids, that all of these α-alkylphenylacetic acids, including α-isopropyl- and α-*t*-butyl- had the *S*-(+) configuration.[8]

However Červinka and Hub[9] subsequently claimed to have chemically interrelated (−)-isopropylphenylacetic acid and hydratropic acid (**1**) of known configuration *via* the common intermediate (−)-2-methyl-3-phenylbutane (**2**) in such a way as to confirm their original assignment of *S*-(−) to **3**.

Horeau and Guetté[10] then related (−)-isopropylphenylacetic acid (**3**) to (+)-isopropylphenylcarbinol (**4**), the configuration of which is generally accepted as *R* based on several lines of indirect but very reliable evidence,[11] and deduced therefrom that (−)-isopropylphenylacetic acid had the *R* configuration.

The configurations of isopropylphenylcarbinol and *t*-butylphenylcarbinol[11] are based on much the same evidence. Recently the generally accepted *S*-(−) configuration of the latter has been challenged[12] based on asymmetric synthesis studies.

We have made extensive use of α-isopropyl- and α-*t*-butylphenylacetic acids and of isopropyl- and *t*-butylphenylcarbinols in our asymmetric reduction studies;[13] it was therefore essential that we determine the absolute configurations of these compounds with certainty. We have therefore undertaken a direct chemical correlation in order to resolve this problem. The interconversions are summarized by formulas **1**–**16**.

Results

We have interrelated (−)-α-*t*-butylphenylacetic acid (**9**) and *S*-(+)-hydratropic acid (**1**) of known absolute configuration by converting them into the common intermediate 2,2-dimethyl-3-cyclohexylbutane (**8**). The process used involves conversion of the carboxyl group of acid **9** into a methyl group, and that of acid **1** into a *t*-butyl group *via* hydrogenolysis of a cyclopropane intermediate by the general procedure first reported by Schleyer and coworkers.[14]

(*S*)-(+)-3-Phenyl-2-butanone (**5**) was prepared by the action of methyllithium on (*S*)-(+)-hydratropic acid[15] (**1**) (Scheme I). This ketone was converted into (*R*)-(+)-3-phenyl-2-methyl-1-butene (**6**), *via* a Wittig

(6) K. Freudenberg, "Die Stereochemie," Franz Deuticke, Leipzig and Vienna, 1933, p 693.

(7) J. Burakevich and C. Djerassi, *J. Amer. Chem. Soc.*, **87**, 51 (1965).

(8) (+)-α-Trifluoromethylphenylacetic acid, which is configurationally related to the other (*S*)-(+)-α-alkylphenylacetic acids, is designated *R*-(+) because CF_3 takes nomenclatural preference over carboxyl according to the Cahn–Ingold–Prelog sequence rule contrary to the other alkyl groups.

(9) (a) O. Červinka and L. Hub, *Z. Chem.*, 423 (1967); (b) *Collect. Czech. Chem. Commun.*, **33**, 1911 (1968); (c) private communication, 1968.

(10) A. Horeau and J. Guetté, *C. R. Acad. Sci. Paris, Ser. C.*, **267**, 257 (1968).

(11) R. MacLeod, F. Welch, and H. S. Mosher, *J. Amer. Chem. Soc.*, **82**, 876 (1960).

(12) O. Červinka, O. Belovský, A. Fabryová, V. Dudek, and K. Grohman, *Collect. Czech. Chem. Commun.*, **32**, 2618 (1967).

(13) J. L. Schmiegel, Ph.D. Thesis, Stanford University, Stanford, Calif., 1967.

(14) (a) C. Woodworth, V. Buss, and P. v. R. Schleyer, *Chem. Commun.*, 569, 570 (1968); (b) J. Jacobus, Z. Majerski, K. Mislow, and P. von R. Schleyer, *J. Amer. Chem. Soc.*, **91**, 1998 (1969).

(15) K. Mislow and J. Brenner, *ibid.*, **75**, 2318 (1953).

reaction using triphenylmethylene phosphorylide. The Simmons–Smith reaction was carried out with the modified procedure of Shank and Schechter[16] to give (*R*)-(−)-1-methyl-1-(α-phenylethyl)-cyclopropane (**7**). Extensive attempts to hydrogenolyze the cyclopropane ring without reducing the aromatic moiety with a variety of catalysts and conditions were unsuccessful. It was therefore necessary to bring about the correlation *via* the cyclohexyl derivative **8**, rather than the phenyl derivative **12**. Cyclopropane **7** was hydrogenated with PtO_2 at 55° in glacial acetic acid to (*S*)-(−)-2,2-dimethyl-3-cyclohexylbutane (**8**).

The second stage of the correlation was completed by reducing (*R*)-(−)-α-*t*-butylphenylacetic acid (**9**) with lithium aluminum hydride to (*R*)-(+)-3,3-dimethyl-2-phenyl-1-butanol (**10**) which gave (*R*)-(+)-3,3-dimethyl-2-phenyl-1-chlorobutane (**11**) upon treatment with thionyl chloride and pyridine. The Grignard reagent was prepared and decomposed with water to give (*R*)-(−)-2,2-dimethyl-3-phenylbutane (**12**), reduction of which with Rh–Al_2O_3 furnished levorotatory hydrocarbon **8**, with the same sign of rotation as that obtained from the (*S*)-(+)-hydratropic acid (**1**).

The configurations of (−)-α-isopropylphenylacetic acid (**3**) and (−)-α-*t*-butylphenylacetic acid (**9**) were linked together through the olefin **6** and its reduction to hydrocarbon **2**. α-Isopropylphenylacetic acid (**3**), enantiomerically pure, was reduced with $LiAlH_4$ to the primary alcohol, treatment of which with thionyl chloride and pyridine produced the chloride. The Grignard reagent was prepared and decomposed with water to give (*R*)-(−)-2-methyl-3-phenylbutane (**2**). Hydrogenation of olefin **6** in the presence of PtO_2 gave the identical hydrocarbon, **2**.

The *R*-(−) acid **9** was converted into (*R*)-(−)-2,2-dimethyl-3-phenyl-4-pentanone (**14**), with methyllithium. We recovered only starting material from the Baeyer–Villiger reaction on this hindered ketone using perbenzoic acid, *m*-chloroperbenzoic acid, or trifluoroperacetic acid. However, (*R*)-(+)-*t*-butylphenylcarbinyl acetate (**15**) was isolated after reaction with persulfuric acid,[17] although it was a minor product. This acetate was cleaved with $LiAlH_4$ to form (*R*)-(+)-*t*-butylphenylcarbinol, (**16**), thus interrelating this carbinol *via* acid **9** and hydrocarbon **8** with hydratropic acid of proven configuration.

In addition, the ORD curves[18] were obtained for the two ketones (+)-**5** and (−)-**14**. These curves are almost exact mirror images, showing that the ketones of opposite configuration give opposite ORD curves in spite of the difference in steric effect of the methyl *vs.* *t*-butyl groups.

To correlate the homologated acid, the Grignard reagent prepared from the (+)-chloride **11** was carbonated to form (*R*)-(+)-β-phenyl-β-*t*-butylpropionic acid[19,20] (**13**).

Discussion

Since (−)-α-*t*-butylphenylacetic acid (**9**) gives (−) hydrocarbon **8**, which in turn is made from known (*S*)-(+)-hydratropic acid (**1**) by a sequence which does not alter the chirality of the asymmetric center, (−)-**9** must have the *R* configuration, and (−)-**8** the *S* configuration as shown in Scheme I. This proves that the previously assigned[4,6] *R* configuration for the (−)-α-*t*-butylphenylacetic acid (**9**) is correct. If the rotations of hydrocarbon **8** prepared by the two routes are adjusted for the enantiomeric purity of the starting acids **1** and **9**, the following result is obtained: **8** from **1**, $\alpha^{24}D$ − 24.2° (neat); **8** from **9**, $\alpha^{23}D$ −22.6° (neat). A similar comparison for **2** gives the rotations following: **2** from **3**, $[\alpha]^{23.5}D$ −27.2° (CC_4), $[\alpha]^{23.5}D$ −20.4° (CH_3OH); and **2** from **6**, $[\alpha]^{23.5}D$ −29.2° (CCl_4). This compares with a value of $[\alpha]D$ −20.6° (CH_3OH), obtained by Červinka and Hub[9] for the same hydrocarbon **2** made from **3** by a slightly different route. The satisfactory agreement of all these values indicates that all the reactions involved in the correlation of these acids have gone with stereochemical integrity.

The interrelation of acid *R*-(−)-**9** to (+)-*t*-butylphenylcarbinol (**16**) by the sequence shown, confirms its *R* configuration as previously assigned by us.[11] The incorrect *R*(−) assignment[12] was based upon an interpretation of the steric course of an asymmetric synthesis which is unwarranted.

The chemical proof of the *R* configuration of the (+)-propionic acid **13** confirms that previously assigned by Almy, Uyeda, and Cram[17] based on the similarity of ORD curves for a derivative of this acid and of a derivative of the known (*R*)-(−)-3-phenylbutyric acid.

The configurational interconnections outlined in the chart also prove the configurations of (*R*)-(+)-isopropylphenylcarbinol as shown and as previously assigned[10,11] and prove that the configuration of α-isopropylphenylacetic acid is *S*-(+) contrary to previous reports,[2,21] but in accord with Horeau's[10] prior assignment.[4] Now that two more α-alkylphenylacetic acids have been proven to have the *S*-(+) configuration, it is almost certain that the configurations of the remaining α-alkyl-substituted phenylacetic acids[4] have been assigned correctly.

Experimental Section

(*S*)-(+)-**3-Phenyl-2-butanone** (**5**).—This ketone was prepared by the method of Mislow and Brenner[15] from hydratropic acid (**1**) which had $[\alpha]^{27}D$ +88.3° (benzene, C 2.96) corresponding to 95.5% excess of the (+) enantiomer. However, the distilled product was found to be impure, and was chromatographed on a silica gel column. The ketone was eluted with benzene and was distilled (102.5–103.5°, 15 mm) to give (*S*)-(+)-3-phenyl-2-butanone (**5**): $[\alpha]^{24}D$ +368° (benzene, C 1.76); ORD maximum $[\theta]_{2180}$ −25,000°, $[\theta]_{2950}$ +25,200° (cyclohexane).

(*R*)-(+)-**2-Methyl-3-phenyl-1-butene** (**6**).—To a solution of 0.0068 mol of *n*-butyllithium in 50 ml of dry ether was added 2.41 g (0.0068 mol) of triphenylmethylphosphonium bromide, and the mixture was stirred at 25° under dry N_2 gas for 3.5 hr. A solution of 1.00 g (0.0068 mol) of ketone **5**, $[\alpha]^{25}D$ +368° (benzene, *c* 1.76), in 10 ml of dry ether was added dropwise. The thick mixture was stirred mechanically and refluxed for 40 hr. Solids were then removed by filtration and washed with ether. The combined filtrates were extracted with water and dried

(16) R. Shank and H. Schechter, *J. Org. Chem.*, **24**, 1825 (1959).

(17) R. Robinson and L. Smith, *J. Chem. Soc.*, 371 (1937).

(18) We wish to thank Dr. Bunnenberg for these ORD measurements which are reported in the experimental section.

(19) J. Almy, R. T. Uyeda, and D. J. Cram, *J. Amer. Chem. Soc.*, **89**, 6768 (1967).

(20) We wish to thank Mr. Robert Whitson for preliminary experiments on this reaction.

(21) By private communication from O. Červinka and L. Hub we are now informed that their sequence[2] actually proves the *S*-(+) configuration and not the *S*-(−) configuration as previously reported.[2] This mistake arose from the presence of an impurity of olefin **6** of opposite rotation in hydrocarbon **2**. NOTE ADDED IN PROOF.—*Cf.* O. Červinka, V. Dudek, and L. Hub, *Z. Chem.*, **9**, 267 (1969).

(Na_2SO_4); solvent was removed under vacuum. The liquid residue was distilled at 95–105° (15 mm) to give 0.70 g of colorless liquid. This mixture of olefin and ketone was separated by preparative glpc on a 6 ft × 0.25 in. 20% Carbowax 4000 column at 170° to give 0.20 g (20% yield) of pure (*R*)-(+)-2-methyl-3-phenyl-1-butene (**6**), $[\alpha]^{25}D$ + 76° (benzene, *c* 1.55). On a later run, a yield of 31% was obtained.

Anal. Calcd for $C_{11}H_{14}$: C, 90.35; H, 9.65. Found: C, 90.39; H, 9.76.

(*R*)-(−)-2-**Methyl-3-phenylbutane** (**2**). **A. From** (*R*)-(−)-α-**Isopropylphenylacetic Acid**[4,13] (**3**).—Acid **3**, $[\alpha]^{24}D$ −62.35° ($CHCl_3$, *c* 4.46), 100% enantiomerically pure, was converted into hydrocarbon **2** by the same method that α-*t*-butylphenylacetic acid (**9**) was converted into 2,2-dimethyl-3-phenylbutane (**12**). The compounds had the followng rotations: (*R*)-(−)-3-methyl-2-phenyl-1-butanol, $\alpha^{22}D$ −11.66° (neat); (*R*)-(−)-3-methyl-2-phenyl-1-chlorobutane, $\alpha^{23}D$ −0.73° (neat); *R*-(−)-2-methyl-3-phenylbutane (**2**), $\alpha^{28}D$ −23.23° (neat), $[\alpha]^{23.5}D$ −27.2° (CCl_4, *c* 2.39), $[\alpha]^{23.5}D$ −20.4° (MeOH, *c* 1.27).

B. From (*R*)-(+)-2-**Methyl-3-phenyl-1-butene** (**6**).—Butene (**6**), 0.12 g, $[\alpha]^{26}D$ +68.5° (benzene, *c* 1.67) in 5 ml of absolute ethanol was added to 0.20 g of prereduced PtO_2 (83.5%, Engelhard Industries) in 10 ml of absolute ethanol and stirred under 1 atm of H_2 for 24 hr at 25°. Filtration and concentration followed by preparative glpc on a 20 ft × 3/8 in. 20% Carbowax 20M TPA at 190°, helium flow rate 60 ml/min, gave 0.055 g of (*R*)-(−)-2-methyl-3-phenylbutane (**2**), retention time 27 min, $[\alpha]^{26}D$ −25.4° (CCl_4, *c* 1.44). Reinjection on the same column indicated less than 0.2% impurity of the olefin **6** in this product which had an ir spectrum identical with that of the same hydrocarbon made by method A.

(*R*)-(−)-1-**Methyl-1-(α-phenylethyl)cyclopropane** (**7**).—Zinc–copper couple,[16] 1.25 g (0.0192 mol), 5.15 g (0.0192 mol) of methylene iodide, and 25 ml of ether were heated to reflux and several crystals of I_2 were added. After this mixture refluxed for 30 min, 1.40 g (9.6 mmol) of olefin **6**, $[\alpha]^{28}D$ +75.4° (benzene, *c* 1.76), $\alpha^{28}D$ +61.98° (neat), was added, and the mixture refluxed overnight. Solids were removed from the cold mixture by filtration through a Celite Super Cel pad. The filtrate was extracted with 5% HCl (3 times with 20 ml) and 10% $NaHCO_3$ (twice with 30 ml) and then dried (Na_2SO_4). The reaction was incomplete as shown by glpc analysis; therefore the ether solution was resubjected to the original reaction conditions with the same amounts of reagents. After the mixture had been heated overnight under reflux and subjected to the same work-up, the product was distilled under vacuum, and purified by preparative glpc on a 10 ft × 3/8 in. 20% Ucon HB 5100 column at 130°, to give 0.60 g (40% yield) of pure **7**, $\alpha^{25}D$ −51.40° (neat).

Anal. Calcd for $C_{12}H_{16}$: C, 89.94; H, 10.06. Found: C, 89.54; H, 10.07.

(*S*)-(−)-2,2-**Dimethyl-3-cyclohexylbutane** (**8**).—A mixture of 0.30 g of **7**, $\alpha^{25}D$ −51.40° (neat), 1.0 g of PtO_2 (83.5%), and 30 ml of glacial acetic acid was shaken under 40 psi of H_2 and heated to 55° for 4 days. The catalyst was removed by filtration and ether was added to the filtrate. This solution was extracted with 10% NaOH and dried (Na_2SO_4), ether was removed under reduced pressure, and the resulting yellow liquid was purified by preparative glpc on a 20 ft × 3/8 in. 30% SE-30 column at 175°, to give **8**, $\alpha^{24}D$ −23.02° (neat).

(*R*)-(+)-3,3-**Dimethyl-2-phenyl-1-butanol** (**10**).[19]—To 5.50 g (0.145 mol) of $LiAlH_4$ in 100 ml of ether was added dropwise at 25° 26.2 g (0.136 mol) of (*R*)-(−)-α-*t*-butylphenylacetic acid (**9**), $[\alpha]^{26}D$ −9.79° [$CHCl_3$, *c* 7.05, 15.6% excess of (−) enantiomer] dissolved in 100 ml of dry ether. The mixture was stirred at 25° for 4 days. Excess hydride was decomposed with saturated Na_2SO_4 solution and 100 ml of 10% NaOH was added. The ether layer was combined with ether extracts, dried ($MgSO_4$), and evaporated under vacuum to leave 24 g (99%) of crude (*R*)-(+)-3,3-dimethyl-2-phenyl-1-butanol (**10**). This carbinol was used without further purification. On a later run, from (+) acid **9** of $[\alpha]^{26}D$ +41.5° ($CHCl_3$, *c* 5.32), 66.3% excess (+) enantiomer, was obtained (−)-carbinol **12** of $[\alpha]^{28}D$ −2.1° ($CHCl_3$, *c* 5.65), mp 75–90°.

(*R*)-(+)-3,3-**Dimethyl-2-phenyl-1-chlorobutane** (**11**).—(*R*)-(+)-3,3-Dimethyl-2-phenyl-1-butanol (**10**) (24.0 g, 0.135 mol), was dissolved in 40 ml of dry pyridine. To this solution was added slowly at 5–10° 14 ml of thionyl chloride. After stirring in an ice bath for 4 hr, the mixture was heated to 90°, and finally to 116° until gas evolution was complete. The mixture was cooled, poured onto ice, and extracted with ether; the ether extracts were washed with saturated $NaHCO_3$ solution and water. The ether layer was dried ($MgSO_4$) and evaporated under vacuum to leave 18.7 g (71%) of crude chloride **11**. This particular sample was distilled after being stored over $NaHCO_3$ for 3.5 years, bp 79–82° (1 mm), to give colorless (*R*)-(+)-3,3-dimethyl-2-phenyl-1-chlorobutane (**11**), $\alpha^{26}D$ +4.56° (neat).

(*R*)-(−)-2,2-**Dimethyl-3-phenylbutane** (**12**).—To 0.144 g (0.0059 g-atom) of sublimed magnesium shavings under dry N_2 was added 1.00 g (0.0051 mol) of (*R*)-(+)-3,3-dimethyl-2-phenyl-1-chlorobutane (**11**), $\alpha^{26}D$ +4.56° (neat), and 20 ml of dry ether. The mixture was heated to reflux and three 0.010-ml portions of 1,2-dibromoethane were added. After refluxing for 3 hr, the reaction was stopped and 4 ml of water was cautiously added. This was followed by 6 ml of 7% HCl. The layers were separated, the aqueous layer was extracted with ether, and the combined ether solutions were dried (Na_2SO_4), and evaporated to 2 ml. The product was isolated by preparative glpc on a 5 ft × 0.25 in. 20% Carbowax 4000 column at 160°, to give 0.57 g (69%) of *R*-(−)-2,2-dimethyl-3-phenylbutane (**12**), $\alpha^{28}D$ −3.42° (neat).

Anal. Calcd for $C_{12}H_{18}$: C, 88.82; H, 11.18. Found: C, 89.06; H, 11.37.

(*S*)-(−)-2,2-**Dimethyl-3-cyclohexylbutane** (**8**).—A mixture of 1.47 g of (*R*)-(−)-2,2-dimethyl-3-phenylbutane (**12**), $\alpha^{28}D$ −3.42° (neat), 1.5 g of 5% Rh–Al_2O_3, and 10 ml of acetic acid–ethanol (1:9) was shaken under 3 atm of H_2 at 25° for 2 days. The catalyst was removed by filtration, and ether was added to the filtrate, which was extracted with 10% NaOH and water. The ether layer was dried (Na_2SO_4) and concentrated under vacuum; the product was isolated by preparative glpc to give 0.50 g (30%) of (*S*)-(−)-2,2-dimethyl-3-cyclohexylbutane (**8**), $\alpha^{23}D$ −3.52° (neat), retention time 9.7 min on a 6 ft × 0.25 in. 20% poly-*m*-phenyl ether 5 ring at 165°; helium flow rate 75 ml/min.

Anal. Calcd for $C_{12}H_{24}$: C, 85.63; H, 14.37. Found: C, 85.87; H, 14.30.

(*R*)-(−)-4,4-**Dimethyl-3-phenyl-2-pentanone** (**14**).—*R*-(−)-α-*t*-Butylphenylacetic acid (**9**), 1.0 g (0.0052 mol), $[\alpha]^{22}D$ −48.2° (absolute EtOH, *c* 1.68), 100% excess (−) enantiomer, was dissolved in 25 ml of dry ether and added slowly to a solution of 0.0176 mol of methyllithium in 20 ml of ether at 25°. After the mixture was stirred at 25° for 20 min and then refluxed for 45 min, it was poured into ice–water. The ether layer was washed rapidly with cold water until neutral and dried (Na_2SO_4), and the solvent was removed under vacuum to leave 0.70 g (70%) of (*R*)-(−)-4,4-dimethyl-3-phenyl-2-pentanone (**14**), >95% pure, $[\alpha]^{25}D$ −275° (CCl_4, *c* 0.835). On a 10 ft × 3/8 in. 20% silicone SE-30 glpc column at 200° and 95 ml/min He, this ketone had a retention time of 44 min. The recovered acid was racemic. Ketone **14** from another run had $[\alpha]^{23}D$ −248° (CCl_4, *c* 1.95); ORD max $[\theta]_{2140}$ +15,800°, $[\theta]_{2060}$ −19,400 (cyclohexane).

(*R*)-(+)-**Phenyl-*t*-butylcarbinyl Acetate** (**15**).—Potassium persulfate (3.98 g, 0.015 mol) was added to a stirred solution of 9.8 g of 98% sulfuric acid and 1.85 g of water at 0°. To this mixture was added 8 ml of absolute ethanol, followed by 0.50 g (0.026 mol) of (*R*)-(−)-4,4-dimethyl-3-phenyl-2-pentanone (**14**), $[\alpha]^{23}D$ −248° (CCl_4, *c* 1.95), in 2.5 ml of absolute ethanol. This mixture was stirred at 0° for 1 hr, then at 25° for 4.5 hr. Water was added, and the solution was extracted with ether. The ether layer was dried (Na_2SO_4) and concentrated under vacuum to give a complex mixture which was separated by preparative glpc on 6 ft × 0.25 in. 20% silicone SF96 at 130°, 90-ml/min helium flow rate. The components of the mixture (at 190°) follow: (retention time, relative area) phenyl *t*-butyl ketone (2.5 min, 3); phenyl-*t*-butylcarbinol (**16**) (3 min, 1); ketone **14** (3.5 min, 1); acetate **15** (3.8 min, 2); and an unidentified solid (7 min, 2). (*R*)-(+)-Phenyl-*t*-butylcarbinyl acetate (**15**), $[\alpha]^{27}D$ +42.3° ($CHCl_3$, *c* 1.66), and the carbinol **16**, $[\alpha]^{28}D$ +11.4° ($CHCl_3$, *c* 2.30), were isolated.

(*R*)-(+)-**Phenyl-*t*-butylcarbinol** (**16**).—(*R*)-(+)-Phenyl-*t*-butylcarbinyl acetate (**15**), 0.035 g (0.00017 mol), $[\alpha]^{27}D$ +42.3° ($CHCl_3$, *c* 1.66), was added to 0.030 g (0.00079 mol) of $LiAlH_4$ in 3 ml of dry ether. The mixture was refluxed 1.5 hr, 10% HCl was added, the layers were separated, and the aqueous phase was extracted with ether. The combined ether extracts were dried (Na_2SO_4) and concentrated to give 0.023 g (82%) of (*R*)-(+)-phenyl-*t*-butylcarbinol (**16**), $[\alpha]^{28}D$ +22.9° ($CHCl_3$, *c* 2.30).

(*R*)-(+)-β-**Phenyl-β-*t*-butylpropionic Acid**[20] (**13**).—Sublimed magnesium, 0.145 g (0.0060 g-atom), and 0.50 g (0.0025 mol) of

R-(+)-3,3-dimethyl-2-phenyl-1-chlorobutane (**11**), $\alpha^{26}D$ +4.54° (neat), were mixed with 15 ml of dry ether and 0.25 ml (0.55 g, 0.0029 mol) of 1,2-dibromoethane was added to start the reaction. After 1.5 hr of reflux, dry CO_2 gas was bubbled through the mixture for 10 min, HCl (10% solution) was added, and the aqueous layer was extracted with ether. The ether extracts were then extracted with 10% NaOH. Acidification of the aqueous layer, extraction with ether, and removal of solvent under vacuum after drying (Na_2SO_4) gave 0.072 g (12%) of crude acid. Sublimation at 85° (0.6 mm) yielded (*R*)-(+)-β-phenyl-β-*t*-butylpropionic acid (**17**), $[\alpha]^{25}D$ +1.74° ($CHCl_3$, *c* 3.16), mp 110–112.5°, reported[22] 114–116°. The nmr spectrum of this material was compatible with the assigned structure.

Registry No.—**2**, 23406-51-1; **5**, 23406-52-2; **6**, 23406-53-3; **7**, 23439-89-6; **8**, 23406-54-4; **9**, 13491-16-2; **11**, 23406-56-6; **12**, 23406-57-7; **14**, 23406-58-8; **15**, 23439-90-9; **16**, 23439-91-0; **17**, 23406-59-9; (*R*)-(−)-3-methyl-2-phenyl-1-butanol, 23406-60-2; (*R*)-(−)-3-methyl-2-phenyl-1-chlorobutane, 23406-61-3.

(22) C. C. Koelsch, *J. Amer. Chem. Soc.*, **65**, 1640 (1943).

Sulfur-Containing Polypeptides. XII. Studies on the Scope and Limitations of the Sulfenylthiocyanate Method as a Route to Cystine Peptides[1,2]

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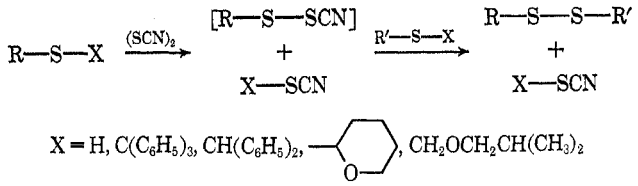
The sulfenylthiocyanate method of disulfide synthesis has been applied to the preparation of 13 cystine peptides containing various amino acid residues. In general no significant side reactions were observed; however, acidic solvents were required for a histidine-containing cystine peptide, and the ω-nitro protective group was necessary for an arginylcystine derivative.

Among the remaining obstacles to the unambiguous synthesis of complex polypeptides is the problem of the "correct pairing" of the sulfur–sulfur bonds of the cystine residues in synthetic polypeptides. At present the final stage of all synthetic routes to polypeptides containing several cystine residues has involved the simultaneous removal of S-protecting groups from cysteine residues and subsequent one-step oxidation. This approach appears to lead to complex mixtures and diminished biological activity.

Several years ago we reported[5] that cystine derivatives could be prepared by employing the sulfenylthiocyanate method discovered by Lecher and Wittwer.[6] These workers had used thiocyanogen to oxidize thiols, and the subsequent recognition that the oxidation could also be performed on appropriate thio ethers[5,7-10] and hemithioacetals[5,11] greatly enhanced the flexibility and apparent applicability of the method to the synthesis of polypeptides containing several cystine residues.



Although these experiments suggest that certain open-chain and cyclic cystine peptides can be prepared *via* the sulfenylthiocyanate method, no information was available on the compatibility of thiocyanogen or the sulfenylthiocyanates of cysteine derivatives with other amino acids. For example, thiocyanogen is known to decompose slowly in the presence of water or alcohols;[12,13] thiocyanogen[14] and sulfenylthiocyanates[15] are also known to react with aliphatic amines to yield amine thiocyanates. In addition, *para*-substituted aromatic amines and phenols undergo ring substitution with thiocyanogen and provide the corresponding 2-iminobenzoazoxoles or 2-iminobenzothioxoles.[12] Although the hydroxyl, phenolic, and amine side chains could always be protected during the preparation of a polypeptide, ring substitution and possible subsequent reactions in tyrosine, tryptophan, and histidine side chains would be a definite possibility. For example, tyrosine, tryptophan, and histidine peptides are cleaved by electrophiles, particularly bromine, N-bromosuccinimide, and cyanogen bromide.[16] Various sulfenyl halides react at the indole 2 position of tryptophan in peptides and proteins but not with the side chains of other amino acids.[17] Finally, methionine is known[16] to suffer cleavage by certain electrophiles, notably cyanogen bromide, and this possibility also warranted examination using thiocyanogen and sulfenylthiocyanates.

In order to evaluate the effects of side chains on the formation of cystine peptides with sulfenylthiocyanates or thiocyanogen, a series of 13 cystine derivatives were prepared; with two exceptions these were of the general structure IV (Table I). The sulfenylthiocyanates II

(1) Preceding paper: R. G. Hiskey, A. M. Thomas, R. L. Smith, and W. C. Jones, Jr., *J. Amer. Chem. Soc.*, **91**, 7525 (1969).

(2) Supported by Research Grants GM-07966 and AM-03416 from the Institute of General Medical Science and the Institute of Arthritis and Metabolic Diseases, National Institutes of Health, U. S. Public Health Service.

(3) Abstracted in part from the Ph.D. dissertation of B. F. Ward, Jr., submitted in partial fulfillment of the requirements for the Ph.D. degree to the University of North Carolina, June 1969.

(4) Ethyl Corp. Fellow, 1968–1969.

(5) R. G. Hiskey and W. P. Tucker, *J. Amer. Chem. Soc.*, **84**, 4789 (1962).

(6) H. Lecher and M. Wittwer, *Chem. Ber.*, **55B**, 1474 (1922).

(7) R. G. Hiskey and D. N. Harpp, *J. Amer. Chem. Soc.*, **87**, 3965 (1965).

(8) R. G. Hiskey, T. Mizoguchi, and E. L. Smithwick, Jr., *J. Org. Chem.*, **32**, 97 (1967).

(9) R. G. Hiskey and M. A. Harpold, *Tetrahedron*, **23**, 3923 (1967).

(10) R. G. Hiskey and R. L. Smith, *J. Amer. Chem. Soc.*, **90**, 2677 (1968).

(11) R. G. Hiskey and J. T. Sparrow, *J. Org. Chem.*, **35**, 215 (1970).

(12) J. L. Wood, *Org. Reactions*, **3**, 242 (1946).

(13) R. G. R. Bacon, *Org. Sulfur Compounds*, **1**, 312 (1961).

(14) L. W. Jones and E. E. Fleck, *J. Amer. Chem. Soc.*, **50**, 2018 (1928).

(15) R. T. Major and L. H. Peterson, *ibid.*, **78**, 6181 (1956).

(16) For a review of these reactions, see B. Witkop, *Advan. Protein. Chem.*, **16**, 237 (1961).

(17) E. Scoffone, A. Fontana, and R. Rocchi, *Biochemistry*, **7**, 971 (1968); A. Fontana, E. Scoffone, and C. A. Benassi, *ibid.*, **7**, 980 (1968); A. Fontana, F. M. Veronese, and E. Scoffone, *ibid.*, **7**, 3901 (1968).