Anal. Calcd for $C_9H_{12}O_2$: C, 71.03; H, 7.95. Found: C, 71.42; H, 8.09.

Lithium–Ammonia Reduction of 2,3-Dihydro-5-methoxy-2-methylbenzofuran (6).—To a magnetically stirred solution of 41 g (0.25 mole) of the dihydrobenzofuran in 50 ml of absolute alcohol and 400 ml of anhydrous liquid ammonia was added 6.5 g (0.94 mole) of lithium in 0.3-g pieces. The addition was carried out over 20 min. Ammonium chloride was added to destroy any excess lithium which still remained after 5 min. The ammonia was allowed to evaporate and the residue was treated with 300 ml of water. The aqueous mixture was extracted three times with ether and the combined extracts were washed once with saturated sodium chloride solution and dried. After concentrating the solution in a flash evaporator, the residue was distilled to give a colorless product, 33.0 g (80%), bp 68–70° (0.3 mm).

The infrared spectrum showed prominent bands at 1645 and 1230 cm^{-1} which are indicative of a vinyl ether. In the nmr spectrum, peaks were observed at 1.30 (3 d, J = 7 cps, $-CH_3$), 1.8–2.9 (6 m, br, $-CH_2-$), 3.45 (3 s, $-OCH_3$), and 4.6 ppm (2 m, one vinyl and one C_2 protons).

Anal. Calcd for $C_{10}H_{14}O_2$: C, 72.26; H, 8.48. Found: C, 72.49; H, 8.55.

Lithium–Ammonia Reduction of 2,3-Dihydro-5-methoxybenzofuran (7).—The reduction was carried out in the same manner as the reduction of 5-methoxybenzofuran (5) in excess alcohol. The yield from 12.4 g (0.083 mole) of the dihydrobenzofuran was 12.4 g (98%).

2,3,4,5,6,7-Hexahydro-2-methylbenzofuran (3) was formed in about 3% yield in the lithium–ammonia reduction of 2,3-dihydro-5-methoxy-2-methylbenzofuran (6). It was isolated from the forerun in the reduced-pressure distillation of the primary product: bp 74–75° (17 mm); ultraviolet (cyclohexane) 226 mμ (ε 3440) and 295 (ε 75); infrared peaks at 1710 and 1200 cm^{-1} (vinyl ether); nmr peaks at 1.23 (3 d, J = 6 cps, $-CH_3$), 1.5–2.9 (10 m, methylene protons), and 4.5 ppm (1 m, a symmetrical multiplet as in 2,3-dihydro-5-methoxy-2-methylbenzofuran).

Anal. Calcd for $C_9H_{14}O$: C, 78.21; H, 10.21. Found: C, 78.03; H, 9.94.

Registry No.—**3**, 10198-31-9; **4**, 13391-27-0; **5**, 13391-28-1; **6**, 13391-29-2; **7**, 13391-30-5; **8**, 13391-31-6; **9**, 13391-32-7; **11**, 13391-33-8; **12**, 13391-34-9; 2-allyl-4-methoxyphenol-, 584-82-7; allyl 4-methoxyphenyl ether, 13391-35-0.

Acknowledgment.—This investigation was supported in part by Grant GM 13452 from the U. S. Public Health Service.

The Resolution and Configuration of α-Substituted Phenylacetic Acids[1a]

COLIN AARON, DAVID DULL, JOEL LARKIN SCHMIEGEL,[1b] DAVID JAEGER, YOKO OHASHI, AND HARRY S. MOSHER

Department of Chemistry, Stanford University, Stanford, California 94305

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Four new optically active substituted phenylacetic acids (α-isopropyl-, α-*t*-butyl-, and α-trifluoromethylphenylacetic acids and α-ethyl-*p*-methoxyphenylacetic acid) have been obtained by classical means and their relative configurations correlated with α-methylphenylacetic acid (hydratropic acid) whose absolute configuration is known. The N-methylthionamide derivatives from the positively rotating acids of this series all have a positive Cotton effect. Furthermore, there is a satisfactory correlation of the rotations of the amides, acids, and anilides within this series. Thus, based upon the positive Cotton effect and Freudenberg displacement rule, it is relatively certain that all of the dextrorotatory acids of this series have the absolute *S* configuration. An unexpected observation of racemization in the synthesis of the amide and anilide derivatives of the α-*t*-butyl- and α-trifluoromethylphenylacetic acids is being investigated further.

We required substantial amounts of α-substituted phenylacetic acids in connection with asymmetric Grignard reduction studies now in progress.[2] These studies, which were designed to determine the effect of increasing the bulk of a substituent group in certain Grignard reagents, required the synthesis, resolution, and determination of absolute configuration of several α-substituted phenylacetic acids. The resolutions were accomplished with reasonable facility by the fractional crystallization of the α-phenylethylamine salts according to the classical procedure.[3] Details for the resolutions are given in the Experimental Section. Properties of these resolved acids and their derivatives are given in Table I along with those of known homologs for comparison.

The amide and anilide were made for each acid, and the properties of these derivatives are listed in Tables I and II. Furthermore, the N-methylthionamide derivative was made in each case and the optical rotatory dispersion determined[4] as recorded in Table III.

The results clearly indicate that all of these (+)-α-alkylphenylacetic acids are configurationally related as evidenced by (1) the uniformly positive Cotton effect of their N-methylthionamide derivatives for the n → π* transition at approximately 340 mμ and (2) with the exception of the α-*t*-butyl case, which is not applicable as discussed below, by the uniform increase in the positive molecular rotations in going from the amide to the acid to the anilide according to the generalized concept of Freudenberg's displacement rule[5] for configurationally related compounds.

The α-*t*-butylphenylacetamide and anilide were not obtained enantiomorphically pure. They were prepared from enantiomorphically pure acid *via* the acid chloride by the same method used for the other members of the series but were found to be extensively racemized and in one experiment completely racemized. Furthermore, some racemization was observed in the preparation of α-trifluoromethylphenylacetamide using aqueous ammonia, although we obtained the pure isomer under anhydrous conditions. The reason for this unexpected racemization is being investigated further. One would expect that the bulky *t*-butyl group would inhibit racemization *via* enol anion formation, as is

(1) (a) We acknowledge with gratitude support for these studies by the National Science Foundation (NSF GP 3888) and the U. S. Public Health Service (GM 05248); (b) National Science Foundation Predoctoral Fellow, 1963–1966.

(2) J. S. Birtwistle, K. Lee, J. D. Morrison, W. A. Sanderson, and H. S. Mosher, *J. Org. Chem.*, **29**, 37 (1964).

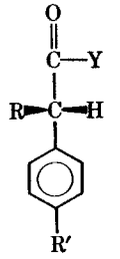
(3) K. Pettersson, *Arkiv Kemi*, **9**, 509 (1956); **10**, 283 (1956).

(4) J. Burakevich and C. Djerassi, *J. Am. Chem. Soc.*, **87**, 51 (1965).

(5) K. Freudenberg, "Die Stereochemie," F. Deuticke Verlag, Leipzig, 1933, p 693.

TABLE I

PROPERTIES OF (*S*)-(+)-α-SUBSTITUTED PHENYLACETIC ACIDS AND DERIVATIVES[a]

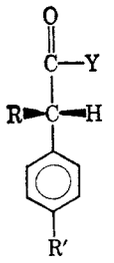


		Acid, Y = OH			Amide, Y = NH_2		Anilide, Y = NHC_6H_5		N-Methylamide		α-Phenylethylamine salt		
R[q]	R′	Mp, °C	$[\alpha]_D$,[f,g] deg (°C)	Solvent	Mp, °C	$[\alpha]_D$,[i] deg (°C)	Mp, °C	$[\alpha]_D$,[f] deg (°C)	(+)isomer, Mp, °C	$[\alpha]_D$,[g] deg (°C)	Confign[o]	Mp, °C	$[\alpha]_D$ deg (°C)
Me[c]	H	*dl*, oil	76.5[c] (25)	$CHCl_3$	*d*, 101–102	46 (25)	*d*, 99–100	120 (25)	35–37[e]	29 (25)[e]	(+) (+)		80 (25)[b,i]
		d, 30–31	81.1[c] (20)	EtOH	*dl*, 97.5[d]	28 (20)							
Et[c]	H	*dl*, oil	95.8 (23)	Neat	*d*, 80.5–81.5	57 (24)	*d*, 79.5–80.5	106[b] (25)	98–99.5[e,h]	20 (25)[e]	(+) (−)		77 (25)[b,i]
		d, oil	78.5 (25)	EtOH									
n-Pr[p]	H	*dl*, oil	76.2 (20)	Neat	*d*, 106–108	50 (25)	*d*, 106.5–108.5	93.5 (25)			(+) (−)		63 (25)[p]
		d, oil	63.4 (25)	EtOH	*dl*, 73–83		*dl*, 116.5–117.5						
i-Pr	H	*dl*, oil	62.5 (25)	$CHCl_3$	*d*, 141–142	56 (24)	*d*, 90–99[l]	65.6 (21)	113–116	53 (25)	(+) (−)	198–200	5.2 (26)[k]
		d, 50.5–51.5	58.6 (30)	EtOH	*dl*, 111–112		*dl*, 132–133[j]						
t-Bu	H	*dl*, 105–108	62.9 (27)	$CHCl_3$	*d*, 114–128[m]	14[l] (21)	*d*, 134–135[l]	53.5[l] (22)	129–132	14.5 (19)	(+) (+)	193–195	22 (27)[f,k]
		d, 141–142	47.7 (18)	EtOH	*dl*, 116–118		*dl*, 111–124[m]						
CF_3	H	*dl*, 77–78	73.4 (24)	$CHCl_3$	*d*, 130–132	56 (21)	*d*, 154–155	151 (27)	135–137	34 (23)	(+) (+)	164–165	27 (24)[i]
		d, 93–94	65.8 (24)	EtOH	*dl*, 107–111								
Et	OMe	*dl*, 62–64	61.1 (22)	$CHCl_3$	*d*, 111–113	23 (24)	*d*, 125–127	80.0 (24)	97–99[n]	3.3 (20)	(+) (+)	138–140	16 (24)[i]
		d, 85–86	64.5 (23)	EtOH									

[a] The rotations reported in this table are all positive and are for the enantiomer with the configuration illustrated. The actual experimental observation may have been made on the (−) isomer (as recorded in the Experimental Section) but has been reported here for the (+) enantiomer. [b] The concentrations at which the rotations were taken were between 1 and 4 g/100 ml in absolute ethanol. [c] K. Pettersson, ref 3; rotations in ethanol, presumably absolute but not specified. Apparently the amount of water in the ethanol significantly affects the rotation as seen in footnote *d*. [d] W. A. Bonner, *J. Am. Chem. Soc.*, **74**, 1034 (1952); rotation in 75% ethanol. [e] See ref 4. [f] These rotations in absolute ethanol, concentration approximately 1–2 g/100 ml. [g] These rotations in chloroform, concentration approximately 2 g/100 ml. [h] From acid of approximately 68% enantiomorphic purity as reported in ref 4. Since the amide was crystallized and the yield was not stated, the enantiomorphic purity of this N-methylamide and corresponding thionamide is unknown. [i] Rotation in absolute ethanol, concentration 1–3 g/100 ml. [j] See A. Hoffman, *J. Am. Chem. Soc.*, **51**, 2542 (1929). [k] Rotations in methanol, concentration of approximately 2 g/100 ml. [l] The enantiomorphic purity of these derivatives is in doubt because of an unknown amount of racemization in their synthesis; thus these represent minimum values. [m] See F. Bodroux and F. Taboury, *Bull. Soc. Chim. France*, [4] **7**, 666 (1910). [n] Prepared from acid of 8.5% enantiomorphic purity. The recrystallized N-methylamide was obtained in 78% yield and thus this derivative has an enantiomorphic purity of approximately 8.5 ± 2%. [o] These properties are for the more insoluble salt of the (+) acid with either the (+) or (−) α-phenylethylamines. [p] K. Pettersson and G. Wildeck, *Arkiv Kemi*, **9**, 333 (1956). [q] Registry No.—(R, R′, Y): Me, H, OH (*dl*), 2328-24-7; (*d*), 7782-24-3; Et, H, OH (*dl*), 7782-29-8; (*d*), 4286-15-1; *n*-Pr, H, OH (*dl*), 7782-21-0; (*d*), 7782-25-4; *i*-Pr, H, OH (*dl*), 13490-68-1; (*d*), 13490-69-2; *t*-Bu, H, OH (*dl*), 13490-70-5; (*d*), 13490-71-6; CF_3, H, OH (*dl*), 13490-72-7; (*d*), 13490-73-8; Me, H, NH_2 (*d*), 13490-74-9; (*dl*), 2328-25-8; Et, H, NH_2 (*d*), 13490-76-1; *n*-Pr, H, NH_2 (*d*), 13490-77-2; (*dl*), 13490-78-3; *i*-Pr, H, NH_2 (*d*), 13490-79-4; (*dl*), 13490-80-7; *t*-Bu, H, NH_2 (*d*), 13490-81-8; (*dl*), 13490-82-9; CF_3, H, NH_2 (*d*), 13490-83-0; (*dl*), 13490-84-1; Me, H, NHC_6H_5 (*d*), 13490-85-2; Et, H, NHC_6H_5 (*d*), 13490-86-3; *n*-Pr, H, NHC_6H_5 (*d*), 13490-87-4; (*dl*), 13490-88-5; *i*-Pr, H, NHC_6H_5 (*d*), 13490-89-6; (*dl*), 13510-00-4; *t*-Bu, H, NHC_6H_5 (*d*), 13490-90-9; (*dl*), 13490-92-1; CF_3, H, NHC_6H_5 (*d*), 13490-91-0; Me, H (N-methylamide), 13490-93-2; Et, H (N-methylamide), 13490-94-3; *i*-Pr, H (N-methylamide), 13490-95-4; *t*-Bu, H (N-methylamide), 13490-96-5; CF_3, H (N-methylamide), 13490-97-6; Me, H (α-phenylethylamine salt), 13490-98-7; Et, H (α-phenylethylamine salt), 13491-02-6; *n*-Pr, H (α-phenylethylamine salt), 13490-99-8; *i*-Pr, H (α-phenylethylamine salt), 13491-00-4; *t*-Bu, H (α-phenylethylamine salt), 13491-01-5; CF_3, H (α-phenylethylamine salt), 13491-03-7; Et, OMe, OH (*dl*), 13491-19-5; (*d*), 13491-20-8; Et, OMe, NH_2 (*d*), 13491-21-9; Et, OMe, NHC_6H_5 (*d*), 13491-04-8; Et, OMe (N-methylamide), 13557-41-0; Et, OMe (α-phenylethylamine salt), 13491-05-9.

TABLE II

MOLECULAR ROTATIONS OF (*S*)-(+)-α-SUBSTITUTED PHENYLACETIC ACIDS, AMIDES AND ANILIDES[a]



R	R′	Amides, Y = NH_2, [M], deg	Acids, Y = OH, [M], deg	Anilides, Y = NHC_6H_5, [M], deg	Ref
t-Bu	H	[27][h]	93	[143][h]	*b*
i-Pr	H	99	104	[166][h]	*b*
n-Pr	H	89	114	237	*c*
Et	H	92	129	253	*d*, *e*
Et	OMe	44[f]	123	215	*b*
CH_3	H	69	122[g]	271	*d*
CF_3	H	113	134	422	*b*

[a] All molecular rotations are from values determined in ethanol. All acids, amides, and anilides reported in this table are dextrorotatory, are configurationally related as indicated in the formula, and have the absolute *S* designation. [b] This paper. [c] A. Fredga, *Arkiv Kemi*, **7**, 241 (1954). [d] K. Pettersson, *ibid.*, **10**, 283 (1956). [e] W. A. Bonner and J. Zderic, *J. Am. Chem. Soc.*, **78**, 3218 (1956). [f] The value of this amide would appear to be low but it has been reconfirmed. [g] This value is calculated from the reported rotation $[\alpha]^{20}D$ +81.1° (EtOH) by A. S. Raper, *J. Chem. Soc.*, **123**, 2558 (1923). E. Eliel and J. Freeman [*J. Am. Chem. Soc.*, **74**, 923 (1952)] have used this value in the interpretation of their work. [h] There is a question concerning the optical purity of these derivatives. Thus, although the sign of rotation is not in doubt, these must be considered minimum values.

observed in the α-*t*-butyl β-diketones.[6] Both the α-*t*-butyl and α-trifluoromethyl derivatives, with opposite inductive effects, show this phenomenon, indicating that it is not electronic in origin. Because of this the assignment of configuration of the α-*t*-butyl homolog at present must rest on the positive Cotton effect of the thionamide derivative.

It is noteworthy that there was no unusual deviation in the rotation for the α-trifluoromethyl derivatives. Thus neither the steric hindrance nor the extreme electronegativity of the trifluoromethyl group greatly perturbs the molecular rotation in this series. It can thus be predicted on this basis that the *rotational rank* (R_D) of the CF_3 group will approximate that of the methyl group in Brewster's[7a] and Marker's[7b] series. The rotational rank of CF_3 *vs.* CH_3 will be discussed in a subsequent paper dealing with trifluoromethylcarbinols.

Since the absolute configuration of (+)-α-methylphenylacetic acid (hydratropic acid), the first member of this series, has been unequivocally established[2] as *S*, and the above evidence indicates that all of the dextrorotatory acids of this series are configurationally related, then they must all have the abolute *S* configuration as shown in Table I.

This does not agree with the assignment of the *R* configuration to the (+)-isopropyl homolog given by Cervinka and Hub[8] based upon an asymmetric transformation involving the reaction of the *dl* acid with optically active (*S*)-(+)-2-methylamino-1-phenylpropane. This latter empirical procedure therefore cannot be relied upon in this series for the assignment of configuration.

Proof that these (+)-α-alkylphenylacetic acids have the same configuration substantiates the conclusion drawn by Halpern and Wesley,[9] based upon the gas chromatographic relative retention times of a series of diastereomeric amides of these acids, and reinforces the value of this method for applications in such a series.

α-Isopropylphenylacetic acid was synthesized in 88% yield from phenylacetic acid by alkylation with isopropyl bromide according to the method of Normet and Angelo[10] using sodium naphthalenide[11] in THF.

The one published method for the synthesis of α-*t*-butylphenylacetic acid by the carbonation of the Grignard reagent from *t*-butylphenylcarbinyl bromide reported[12] a crude yield of 13% and appeared quite unsatisfactory. The main product reported was 1,2-diphenyl-1,2-di-*t*-butylethane, resulting from coupling of the Grignard reagent. By using the Grignard reagent from the corresponding chloride instead of bromide, tetrahydrofuran solvent instead of ether, and carbonation under pressure, the yield was increased to 80%.

Several methods were investigated for the synthesis of α-trifluoromethylphenylacetic acid. Although α-hydroxy-α-trifluoromethylphenylacetic acid could be made readily *via* the cyanohydrin procedure, contrary to a report in the literature,[13] various attempts at reduction with phosphorus and hydrogen iodide[14] were completely unsuccessful.

The synthetic approach *via* the Wittig reaction proved successful as well as general.[15] Methoxymethylenetriphenylphosphonium chloride[16] (II) and phenyl trifluoromethyl ketone (I) when treated with sodium ethoxide gave the enol ether III which was contaminated with ethyl benzoate. This ethyl benzoate presumably was formed by a haloform-type reaction on the starting ketone. The crude mixture was hydrolyzed to the crude aldehyde IV which was oxidized directly with potassium permanganate to give the purified acid in an over-all yield of about 35% (Scheme I).

The resolutions were carried out on each of these α-substituted acids by fractional crystallization of the α-phenylethylamine salts from aqueous ethanol or methanol. With the exception of the α-isopropyl case, the dextrorotatory acid gave the more insoluble salt with the dextrorotatory amine. In each case the pure isomer melted sharply at a higher point than the racemic compound. The progress of the resolutions was readily followed by melting point of the salts, and the completeness of the resolution has also been verified

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(7) (a) J. H. Brewster, *J. Am. Chem. Soc.*, **81**, 5477 (1959); (b) R. E. Marker, *ibid.*, **58**, 976 (1936).

(8) O. Cervinka and L. Hub, *Chem. Commun.*, 761 (1966).

(9) B. Halpern and J. W. Wesley, *ibid.*, 237 (1967).

(10) (a) H. Norment and B. Angelo, *Bull. Soc. Chim. France*, 810 (1962); (b) also see D. J. Cram, F. A. Abd Elhafez, and H. L. Nyquist, *J. Am. Chem. Soc.*, **76**, 22 (1954); (c) see Table I, footnote *m*; (d) see Table I, footnote *j*.

(11) L. Horner and H. Gusten, *Ann.*, **652**, 99 (1962).

(12) J. H. Ford, C. D. Thompson, and C. S. Marvel, *J. Am. Chem. Soc.*, **57**, 2619 (1935).

(13) J. H. Simons and E. O. Rambler, *ibid.*, **65**, 390 (1943).

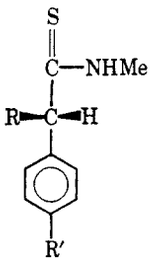
(14) K. Miescher and J. R. Billeter, *Helv. Chim. Acta*, **22**, 601 (1939).

(15) D. Dull, I. Baxter, and H. S. Mosher, *J. Org. Chem.*, **32**, 1622 (1967).

(16) G. Wittig and M. Schlossen, *Ber.*, **94**, 1373 (1961).

TABLE III

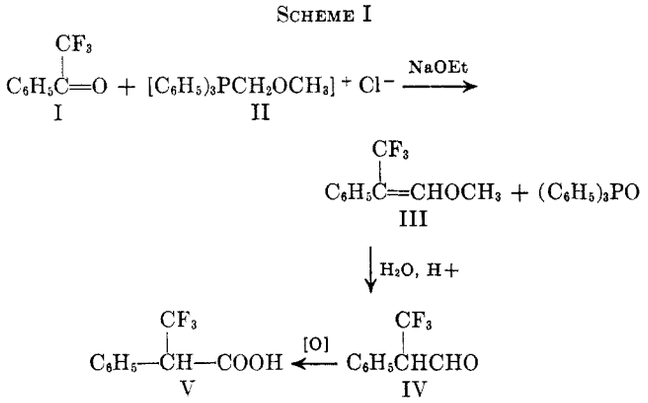
OPTICAL ROTATORY DISPERSION DATA FOR (+)-α-SUBSTITUTED N-METHYLPHENYLTHIONAMIDES[a]



R	R′	Registry No.	Peak [M],[e] deg	Peak mμ	Trough [M],[e] deg	Trough mμ	Peak [M],[e] deg	Peak mμ	Cotton effect	λmax, mμ, n → π* band	Ref	Absolute confign
Me	H	13491-06-0	+1720	365	−1002	318			+	342	*b*	*S*
Et	H	13491-07-1	+870	369	−579	320			+	340	*b*	*S*
i-Pr	H	13491-08-2	+1680	367	−1220	325	918	285	+	340	*c*	*S*
t-Bu	H	13491-09-3	+1364	373	−792	330	1590	283	+	350	*c*	*S*
CF_3	H	13491-10-6	+157	375	−52	335	*d*		+	340	*c*	*R′*
Et	OMe	13491-11-7	+770	360	−544	318	*d*		+	325	*g*	*S*

[a] We are indebted to Mrs. Ruth Records for these ORD measurements which were made in methanol solution on a Japan Spectroscopic Co. Automatic recording spectropolarimeter. [b] See ref 4. [c] This paper. [d] There was strong absorption below 300 mμ which prevented obtaining the rotation at lower wavelengths. [e] There was undoubtedly racemization in the synthesis of these thionamides, and thus no significance can be attached to the magnitude of the rotations but the sign of the Cotton effect is of course valid and definitive. [f] According to the Cahn, Ingold, Prelog rules for the *R* and *S* configuration convention [R. S. Cahn, C. Ingold, and V. Prelog, *Angew. Chem. Intern. Ed. Engl.*, **5**, 385 (1966) errata 511] CF_3 takes sequential preference over the phenyl group, while for all other alkyl groups in the series the reverse holds. [g] The maximum possible enantiomorphic purity of this sample is about 10%. Because of racemization, it could be considerably less. See Experimental Section.

SCHEME I



in the α-*t*-butyl case by Halpern and Wesley by a gas chromatographic separation of diasteriomeric amides derived from (+)-2-methyl-amino-1-phenylpropane.[17]

Experimental Section

α-Isopropylphenylacetic Acid (2-Phenyl-3-methylbutanoic Acid).[10b]—Sodium naphthalenide[11] was prepared by stirring a mixture of sodium (55 g, 2.3 g-atoms), naphthalene (294 g, 2.3 moles), and tetrahydrofuran (2 l. dried by distillation from lithium aluminum hydride) for 8 hr. This solution was rapidly added to a vigorously stirred solution of phenylacetic acid (136 g, 1 mole) in tetrahydrofuran (2 l.) at a rate which resulted in spontaneous refluxing. After stirring for 4 hr, isopropyl bromide (180 g, 1.5 moles) was added over a 1-hr period and the reaction mixture was stirred overnight. Water (500 ml) was added and the mixture extracted with 10% sodium carbonate (1 l.) and then with water (2 l.). The basic aqueous extracts were washed with ether and acidified with hydrochloric acid. The mixture was extracted with ether, and the ether extracts were dried ($MgSO_4$) and distilled to give α-isopropylphenylacetic acid (157 g, 88% yield), bp 132–134° (2 mm). Gas chromatography (Dow 710 silicone oil column 10 ft × 0.25 in., 190°, 40 cc of He/min, retention time 23 min) indicated better than 98% purity.

α-Trifluoromethylphenylacetic Acid (2-Phenyl-3,3,3-trifluoropropanoic Acid).—A solution of 104 g (0.30 mole) of methoxymethylenetriphenylphosphonium chloride[16] in 100 ml of anhydrous ethanol (distilled from magnesium ethoxide) was cooled to 15° in a 500-ml flask equipped with a mechanical stirrer, condenser, dropping funnel, and nitrogen atmosphere. Sodium ethoxide, prepared from 6.88 g (0.30 g-atom) of sodium and 100 ml of anhydrous ethanol, was added with stirring. After the mixture had warmed to 20° over a 45-min period, 57.7 g (0.33 mole) of phenyl trifluoromethyl ketone (Columbia Organic Chemicals Co.) was added and the reaction mixture stirred at 55° for 15 hr. The mixture was cooled, the salt removed by filtration, and the ethanol removed by fractional distillation under reduced pressure. The residue was ether extracted and the extracts were distilled to give 48.9 g, bp 78–90° (3 mm). Gas chromatographic analysis (Carbowax 20 M, 10 ft × 0.25 in., 185°, 60 cc of He/min) indicated three components with retention times of 11, 13, and 17 min, respectively. That with retention time of 13 min constituted about 18% of the mixture and was identified by the peak-enhancement technique and from the isolation of a sample by gas chromatography as ethyl benzoate. The infrared spectrum of samples isolated from the other two peaks indicated that they were the isomeric enol ethers produced in a calculated combined yield of 66%.

Without purification, 47.6 g of this mixture was hydrolyzed with 65 g of water and 152 g of concentrated sulfuric acid at 60° for 2 hr. The cooled hydrolysis mixture was poured onto ice and extracted with ether; the ether extracts were washed sequentially with saturated salt solution, sodium bicarbonate solution, and salt solution. Distillation of the dried ($MgSO_4$) extracts gave 40.8 g, bp 90–100° (20 of mm), a crude α-trifluoromethylphenylacetaldehyde which was still contaminated with ethyl benzoate. The 2,4-dinitrophenylhydrazone from ethanol melted at 132–133°.

Anal. Calcd for $C_{15}H_{11}F_3N_4O_4$: C, 48.92; H, 3.01. Found: C, 48.80; H, 2.77.

The above aldehyde (40.8 g) was oxidized in a solution of sulfuric acid (46.6 g), water (200 g), and acetone (60 ml) at 5° by the addition of potassium permanganate (22 g) over a 2-hr period. After an additional 2 hr at 3°, the excess permanganate was destroyed with sodium bisulfite (16 g), and the mixture was extracted with ether. Extraction of these ether extracts with sodium bicarbonate solution followed by acidification, reextraction, drying ($MgSO_4$), and evaporation gave a crystalline residue which was recrystallized from hexane to give 20 g of α-trifluoromethylphenylacetic acid: mp 77–78°; infrared absorption bands, 2800–3400 (OH), 1720 (C=O), 1170 and 1120 (CF_3) cm^{-1}.

(17) We are indebted to B. Halpern and J. Wesley, Stanford University School of Medicine, for this determination which will be included by them in a forthcoming publication.

Anal. Calcd for $C_9H_7F_3O_2$: C, 52.94; H, 3.45. Found: C, 53.02; H, 3.52.

α-Ethyl-*p*-methoxyphenylacetic Acid (2-*p*-Methoxyphenylbutanoic Acid).—By using the same procedure as described for α-isopropylphenylacetic acid, but substituting *p*-methoxyphenylacetic acid (166 g) and ethyl bromide (124 g), there was obtained a crude yield of α-ethyl-*p*-methoxyphenylacetic acid as a yellow oil, bp 142–144° (1 mm), which solidified on standing. This was recrystallized from petroleum ether (bp 55–85°) to give a product (188 g, 96% crude yield), mp 51–58°, which by gas chromatographic analysis (Dow 710 column, 10 ft × 0.25 in., 190°, 40 cc of He/min) was shown to consist of 88% desired α-ethyl-*p*-methoxyphenylacetic acid (retention time, 16.6 min) and 12% unreacted starting material (retention time, 10.2 min).

When this same procedure was used starting with *p*-methoxyphenylacetonitrile (294 g) and ethyl bromide (240 g), the corresponding nitrile which was obtained was resistant to hydrolysis. After vigorous refluxing for 140 hr with concentrated hydrochloric acid, which was replenished twice daily during this period, α-ethyl-*p*-methoxyphenylacetic acid (141 g, 36.5% yield) which was 97% pure was obtained. Recrystallization from petroleum ether (bp 55–85°) gave a purified product, mp 62–64°. The melting point reported for this compound made from α-phenyl butyric acid *via* nitration, reduction, and diazotization is 65–67°.[18]

α-*t*-Butylphenylacetic Acid (2-Phenyl-3,3-dimethylbutanoic Acid).—*t*-Butylphenylcarbinyl chloride (α-phenylneopentyl chloride, 100 g), prepared in 90% yield by the method of Winstein and Morse[19] from *t*-butylphenylcarbinol and thionyl chloride, was shown by nmr to contain no more than 2% impurity. This product was converted to the Grignard reagent in tetrahydrofuran (500 ml distilled from lithium aluminum hydride) with magnesium (15 g, stock Baker and Adamson grade). The reaction was conducted under purified nitrogen and was initiated by the addition of a small amount of 1,2-dichloroethane. The Grignard solution was transferred under nitrogen to the pressure bottle of a Parr hydrogenation apparatus which was charged with dry carbon dioxide. The Grignard reagent was then shaken under a carbon dioxide atmosphere at a pressure of 30–45 psi, until the theoretical amount had been absorbed (about 45 min). The mixture became hot and it was necessary to interrupt the shaking periodically in order to allow the reaction to cool. The carbonation mixture was poured onto ice and hydrochloric acid and then was ether extracted. The ether extracts were in turn extracted with 2 *N* aqueous sodium hydroxide. Upon acidification and extraction of the alkaline extracts there was obtained crude α-*t*-butylphenylacetic acid (84.5 g, 80.5% yield) which was recrystallized from petroleum ether (bp 60–70°) to give 78 g of acid, mp 105–108°. From the neutral fraction there was recovered 8.9 g of material, mp 179–181°, which was identified as the Grignard coupling product, 1,2-diphenyl-1,2-di-*t*-butylethane.[12]

The yields were considerably less when ether solvent was used, when carbonation was done by pouring onto Dry Ice, or when gaseous carbon dioxide was introduced above the surface of the Grignard reagent. The use of highly purified sublimed magnesium did *not* improve the yield.

Resolution of α-Isopropylphenylacetic Acid.—*dl*-α-Isopropylphenylacetic acid (461 g), (+)-α-phenylethylamine (313 g, $\alpha^{27}D$ +37.8, neat, l = 1), and 63% aqueous ethanol (10 l.) were warmed and allowed to cool slowly. The 353 g of salt which separated was recrystallized four times from 63% aqueous ethanol (6, 5.5, 5, and 4.5 l., respectively) to give 272 g of salt, mp 198–200°, $[\alpha]^{26}D$ −5.2 (CH_3OH, c 2.62). Regeneration with 10% sulfuric acid at 0° gave, after extraction, drying, and distillation, 153.5 g of (−)-α-isopropylphenylacetic acid, bp 132–133° (3.5 mm), which solidified, mp 50.5–51.5°, $[\alpha]^{24}D$ −62.4 ($CHCl_3$, c 4.46). The mother liquors were concentrated, and the partially active (+) acid regenerated in the same way to give 261 g, $[\alpha]^{24}D$ +36.01 ($CHCl_3$, c 3.86). This acid was treated with (−)-α-phenylethylamine ($\alpha^{28}D$ −36.6, neat, l = 1) and the process repeated to obtain the pure acid, $[\alpha]^{26}D$ +62.5 ($CHCl_3$, c 2).

The resolution was also attempted with cinchonidine. α-Isopropylphenylacetic acid (50 g) and cinchonidine (76 g) were heated in 1.5 l. of 60% methanol. The 52 g of salt which was obtained on cooling was recrystallized four times from methanol to give 17 g of salt, mp 136–137.5°, $[\alpha]^{29}D$ −68.5, which upon regeneration gave an incompletely resolved acid, 5.6 g, $[\alpha]^{27}D$ +48.7° ($CHCl_3$, c 3). Cinchonidine was obviously inferior to α-phenylethylamine for this resolution. Although we were unable to obtain a crystalline cinchonidine salt from the resolved (−)-isopropylphenylacetic acid, the (+) isomer, $[\alpha]^{25}D$ +62.3 ($CHCl_3$, c 3), gave a crystalline cinchonidine salt from which, after several recrystallizations, the original (+) acid was regenerated without significant change in rotation. This gives added evidence that the resolution was complete.

Resoluton of α-*t*-Butylphenylacetic Acid.—*dl*-α-*t*-Butylphenylacid, 127.5 g, was heated with (+)-α-phenylethylamine, 80.7 g, $\alpha^{26}D$ +37.6 (l = 1, neat), in 3 l. of 70% aqueous ethanol, and the solution was allowed to cool slowly to give 170 g of salt. Six successive crystallizations of this salt from 70% aqueous ethanol gave 31.5 g, mp 193–195°, $[\alpha]^{27}D$ +21.2 (CH_3OH, c 3.5) which upon treatment with 25% sulfuric acid in the cold gave 17.2 g of acid, mp 141–142°, $[\alpha]^{27}D$ +62.9 ($CHCl_3$, c 7). More dextrorotatory acid was recovered by fractional crystallization of the salts from the mother liquors. Regeneration of the noncrystalline mother liquors gave impure (−) acid, mp 103–110°, $[\alpha]^{24}D$ −7.7 ($CHCl_3$, c 3). This was converted to the pure (−) acid, $[\alpha]^{26}D$ −62.9 ($CHCl_3$, c 5), by fractional crystallization of the salt prepared from the enantiomeric (−)-α-phenylethylamine. It was determined in this portion of the resolution that methanol was superior to 70% ethanol as a solvent for the fractional crystallization.

Resolution of α-Trifluoromethylphenylacetic Acid.—A solution of 100 g of the racemic acid in 2:1 ethanol–water was mixed with 59.4 g of (−)-α-phenylethylamine, $\alpha^{12}D$ −37.43 (l = 1, neat). The salt, which formed immediately, was crystallized three times from 2:1 ethanol–water using 1.5–2.0 ml of solvent for each gram of salt. This was twice recrystallized without changing its properties. A fraction (20.2 g), $[\alpha]^{24}D$ −27.4 ± 0.5 (ethanol, c 3.86), mp 164–165°, was decomposed in 2:1 water-concentrated hydrochloric acid to give, after isolation and recrystallization from hexane, 11.9 g of material, $[\alpha]^{24}D$ −71.4 ± 0.5 ($CHCl_3$, c 2.24), mp 93–94°. In this manner 22 g of material was obtained with specific rotation greater than 70°. The remaining salt fractions were decomposed in the above manner, and the isolated acid was treated with (+)-α-phenylethylamine, $\alpha^{24}D$ +37.56 (l = 1, neat). Recrystallization of this salt gave a fraction (40.0 g) with $[\alpha]^{21}D$ +25.8 ± 0.8 (ethanol, c 2.59). Decomposition of the salt gave 23.7 g of acid, $[\alpha]^{24}D$ +73.4 ± 0.5 ($CHCl_3$, c 4), $[\alpha]^{24}D$ +65.8 ± 1.7 (ethanol, c 1), mp 93–94°, after hexane crystallization

Resolution of α-Ethyl-*p*-methoxyphenylacetic Acid.—Fractional crystallization from 80% ethanol of the cinchonidine salt prepared from 605 g of the acid and 940 g of cinchonidine gave a salt, mp 147–148°, $[\alpha]^{24}D$ −62.9 (ethanol, c 4), from which the acid was regenerated with 25% sulfuric acid and recrystallized from petroleum ether (bp 55–85°) to give the dextrorotatory acid, mp 85–86°, $[\alpha]^{23}D$ +64.76 (ethanol, c 4), 152 g. The product of this acid with (+)-α-phenylethylamine was recrystallized twice from aqueous ethanol to give a salt, $[\alpha]^{24}D$ +14.45° (ethanol, c 4), from which the acid was regenerated with essentially unchanged properties, mp 85–86°, $[\alpha]^{23}D$ +64.46 (ethanol, c 4).

(*R*)-(−)-α-Isopropylphenylacetamide.—A mixture of (*R*)-(−)-α-isopropylphenylacetic acid, $[\alpha]^{30}D$ −58.6 ± 1.8 (absolute ethanol, c 1.1), 1.60 g (0.009 mole), and redistilled thionyl chloride, 9.6 g, (0.8 mole) was refluxed in an oil bath for 40 min; then the excess thionyl chloride was removed under vacuum, and the residual acid chloride taken up in benzene (10 ml) and treated with cold, concentrated ammonium hydroxide, 2.5 ml (0.038 mole). The reaction mixture was diluted with water and benzene; the benzene layer separated and was washed several times with water, dried ($MgSO_4$), and evaporated under reduced pressure to give the crude amide which was recrystallized three times from 50% ethanol–water: 0.68 g, (43% yield), mp 132–140.5°. Since this material was not pure, it was dissolved in ether and the solution was washed with 5% bicarbonate solution and then with water, dried ($MgSO_4$), and evaporated. The residue recrystallized from 50% ethanol–water to give 0.30 g, mp 141–142°, $[\alpha]^{24}D$ −55.9 ± 2.9 (absolute ethanol, c 1.04). The *dl* compound is reported[10c] to melt at 111–112°.

Anal. Calcd for $C_{11}H_{15}NO$: C, 74.54; H, 8.53; N, 7.90. Found: C, 74.58; H, 8.48; N, 7.93.

(*R*)-(−)-α-Isopropylphenylacetanilide.—A mixture of (*R*)-(−)-α-isopropylphenylacetic acid, $[\alpha]^{30}D$ −58.6 ± 1.8 (absolute

(18) O. S. Madaeva, N. M. Goncharova, and V. I. Maksimov, *Zh. Obshch. Khim.*, **23**, 472 (1953); *Chem. Abstr.*, **48**, 5136*d* (1954).

(19) S. Winstein and B. K. Morse, *J. Am. Chem. Soc.*, **74**, 1138 (1952).

ethanol, *c* 1.14), 0.99 g (0.0056 mole), and thionyl chloride, 8 ml (0.111 mole), was refluxed on the steam bath for 40 min and the excess thionyl chloride was removed under reduced pressure. A solution of the residue in benzene, 10 ml, was treated with freshly distilled aniline, 2 ml (0.025 mole), in 10 ml of benzene by mixing in an ice bath. Water, 30 ml, and benzene, 20 ml, were added; the layers separated and the benzene layer was washed three times with cold 10% hydrochloric acid and three times with water and dried ($MgSO_4$). The benzene was removed and the residue recrystallized four times from hexane–benzene to give white fibrous crystals, mp 90.5–98.5°, $[\alpha]^{21}D$ −65.6 ± 1 (absolute ethanol, *c* 3.3), 0.72 g (52%). The *dl* compound is reported[10d] to melt at 132–133°.

Anal. Calcd for $C_{17}H_{19}NO$: C, 80.57; H, 7.56; N, 5.53. Found: C, 80.78; H, 7.60; N, 5.62.

(*R*)-(−)-N-Methyl-α-isopropylphenylthionacetamide.—A mixture of 440 mg of N-methyl-α-isopropylphenylacetamide, mp 113–126°, $[\alpha]^{25}D$ −53.1 ± 1.6 ($CHCl_3$, *c* 1.9), prepared as described above for the unsubstituted amide from (−) acid, $[\alpha]^{24}D$ −62.4 ($CHCl_3$, *c* 4.46), 226 mg of sulfurated potash (Allied Chemical Co.), 248 mg of phosphorus pentasulfide (Matheson, Coleman and Bell), and 10 ml of *m*-xylene was heated over a 30-min period to 105° and held at this temperature for 0.5 hr. The supernatant liquid was removed and the residue was digested with refluxing xylene for an additional 30 min. The combined xylene extracts were evaporated to dryness under reduced pressure; the residue was dissolved in hot benzene and chromatographed on silica gel (20 g, 60–200 mesh, Davidson Chemical) by elution first with benzene and then with benzene–ethyl acetate. The product (80% yield) was recrystallized from hexane–benzene, 342 mg, mp 103.5–105.5°, $[\alpha]^{19}D$ −24.7 ± 2 (CH_3OH, *c* 1). The ORD measurements are given in Table III.

Anal. Calcd for $C_{12}H_{17}NS$: C, 69.51; H, 8.27; N, 6.76. Found: C, 69.59; H, 8.42; N, 6.47.

α-*t*-Butylphenylacetamide.—A solution of (*S*)-(+)-α-*t*-butylphenylacetic acid, mp 141–142°, 292 mg, $[\alpha]^{27}D$ +62.9 ($CHCl_3$, *c* 7), $[\alpha]^{18}D$ +47.7 (absolute ethanol, *c* 1.4), and thionyl chloride, 3 ml, was refluxed for 45 min and the excess thionyl chloride was removed under reduced pressure to give a liquid residue which was dissolved in benzene (10 ml). This solution was shaken with ammonium hydroxide, 2 ml, and the amide was purified by mixing with benzene (35 ml) and extracting the benzene solution successively with water, sodium bicarbonate solution, and water. The dried ($MgSO_4$) benzene extracts were evaporated to dryness and the residue (96% crude yield) was recrystallized three times from 1:1 ethanol–water and twice from petroleum ether–benzene to give an amide, mp 114–128°, $[\alpha]^{21}D$ +13.8 ± 2.1 (absolute ethanol, *c* 0.94), which was not stereochemically pure as evidenced by the wide melting range.

Anal. Calcd for $C_{12}H_{17}NO$: C, 75.35; H, 8.96; N, 7.32. Found: C, 75.05; H, 8.73; N, 7.12.

Evaporation of the ethanol–water filtrates afforded white crystals, mp 116–118.5°, which had zero rotation within experimental error.

When this preparation was repeated using the reaction of a benzene solution of the acid chloride with gaseous ammonia instead of aqueous ammonia and working-up the reaction mixture without washing with bicarbonate solution, a product was obtained (68% yield), $[\alpha]^{22}D$ +5.4 ± 0.6 (absolute ethanol, *c* 3.35), mp 114–119°.

α-*t*-Butylphenylacetanilide.—(*S*)-(+)-α-*t*-Butylphenylacetic acid, mp 140.5–141.5°, $[\alpha]^{18}D$ +47.7 ± 1.4 (absolute ethanol, *c* 1.4), 0.190 g, and thionyl chloride, 2.8 ml (0.039 mole), were refluxed for 45 min and the mixture was evaporated to dryness under reduced pressure. The residue in benzene was treated with a benzene solution of aniline 1.2 ml (0.013 mole). Heat was liberated and after a few minutes the mixture was diluted with benzene; the benzene layer was successively washed with dilute hydrochloric acid, water, sodium bicarbonate, and water. The dried ($MgSO_4$) benzene layer was evaporated to dryness and and the residue, 78% yield, was twice crystallized from petroleum ether–benzene, mp 129.5–134.0°, $[\alpha]^{22}D$ +9.7 ± 2.4 (absolute ethanol, *c* 0.8). A third crystallization gave a product with a higher melting point, 133.0–135.5°, and a lower rotation, $[\alpha]^{23}D$ +3.4 ± 2.3 (absolute alcohol, *c* 0.87), indicating that the *dl* compound was preferentially crystallizing.

Anal. Calcd for $C_{18}H_{21}NO$: C, 80.86; H, 7.92; N, 5.24. Found: C, 80.61; H, 7.94; N, 5.25.

White crystals of the partially active anilide, mp 111–124°, $[\alpha]^{20}D$ +53.5 ± 7 (absolute ethanol, *c* 0.4), were obtained from the filtrates.

A repetition of this preparation which was worked up without the acidic and basic washes gave a 54% yield of racemic product, mp 134–135°, $\alpha^{22}D$ −0.01 ± 0.02 (absolute ethanol, *c* 3.435).

(*S*)-(+)-N-Methyl-α-*t*-butylphenylacetamide.—A solution of the acid chloride (prepared from 0.5 g of acid, $[\alpha]^{27}D$ +62.9 ($CHCl_3$), and 10 ml of thionyl chloride) was added with stirring to 40% cold aqueous methylamine. The product was isolated in the usual manner to give, after recrystallization from hexane–benzene, 441 mg (82%) of material, mp 129–132°, $[\alpha]^{19}D$ +14.5 ± 1.2 ($CHCl_3$, *c* 1.65).

Anal. Calcd for $C_{13}H_{19}NO$: C, 76.05; H, 9.32; N, 6.82. Found: C, 75.90; H, 9.13; N, 7.01.

(*S*)-(+)-N-Methyl-α-*t*-butylphenylthionacetamide.—A mixture of 388 mg of the amide, 222 mg of sulfurated potash (Allied Chemical), 279 mg of phosphorus pentasulfide (Matheson, Coleman, and Bell), and 10 ml of *m*-xylene was stirred and heated to 110° over a period of 45 min and held at this temperature for 45 min. The supernatant liquid was filtered and the residue was reheated with 10 ml of *m*-xylene for 30 min. The combined filtrates were reduced to dryness and the residue was heated with benzene and filtered to remove sulfur. The filtrate was chromatographed on 20 g of silica gel (Davison Chemical, 60–200 mesh) by elution first with benzene, then with 3:1 benzene–ethyl acetate, to give 374 mg (88%) of a slightly yellow solid. Repeated recrystallization from hexane–benzene gave 189 mg of large prisms, mp 139–143°, optically inactive between 600 and 300 mμ. The filtrates were reduced to dryness and the residue was recrystallized to give 121 mg, mp 127–139°, $[\alpha]^{17}D$ +25.8 ± 1.0 (*c* 1.86, MeOH). The two fractions gave identical infrared spectra with bands at 3370, 2960, and 1520 cm^{-1}. The ORD data are reported in Table III.

Anal. Calcd for $C_{13}H_{19}NS$: C, 70.53; H, 8.65; N, 6.32. Found: C, 70.86; H, 8.60; N, 6.21.

(*R*)-(−)-α-Trifluoromethylphenylacetamide [(*R*)-(−)-2-Phenyl-3,3,3-trifluoropropanamide].—A benzene solution of the acid chloride, prepared in the usual way from 0.5 g of acid, $[\alpha]^{24}D$ −71.4 ($CHCl_3$ *c* 4), and 10 ml of thionyl chloride, was saturated with dry ammonia. Isolation of the amide in the usual manner and recrystallization from hexane–benzene gave 0.20 g (40%) of needles, mp 130–132°, $[\alpha]^{19}D$ −55.6 ± 1.2 (absolute ethanol, *c* 1.7).

Anal. Calcd for $C_9H_8F_3NO$: C, 53.20; H, 3.96; N, 6.89. Found: C, 52.99; H, 4.10; N, 6.79.

(*S*)-(+)-α-Trifluoromethylphenylacetanilide [(*S*)-(+)-N-Phenyl-2-phenyl-3,3,3-trifluoropropanamide].—A benzene solution of the acid chloride, prepared in the usual way from 0.5 g of acid, $[\alpha]^{21}D$ +66.5 ($CHCl_3$), and 5 ml of thionyl chloride, was added to a chilled solution of excess aniline in benzene. Isolation of the product in the usual manner and recrystallization from benzene–hexane gave 0.4 g (58%) of colorless needles, mp 154–155°, $[\alpha]^{27}D$ +151.5 ± 1.2 (absolute ethanol, *c* 1.65).

Anal. Calcd for $C_{15}H_{12}F_3NO$: C, 64.51; H, 4.33; N, 5.01. Found: C, 64.57; H, 4.23; N, 4.93.

(*S*)-(+)-N-Methyl-α-trifluoromethylphenylacetamide [(*S*)-(+)-N-Methyl-2-phenyl-3,3,3-trifluoropropanamide].—A benzene solution of the acid chloride, prepared in the usual manner from 1.0 g of acid, $[\alpha]^{24}D$ +73.4 ($CHCl_3$), and 10 ml of thionyl chloride, was added, with stirring and cooling, to 30 ml of benzene saturated with methylamine. After 15 min the mixture was poured on ice and concentrated hydrochloric acid. The mixture was extracted with ether and the extracts were washed with bicarbonate solution and dried ($MgSO_4$). Removal of the ether and recrystallization of the residue from hexane–benzene gave 0.6 g (58%) of colorless needles, mp 135–137° (*dl* material made from *dl* acid, mp 113–115°), $[\alpha]^{23}D$ +33.8 ± 0.8 ($CHCl_3$, *c* 1.30).

Anal. Calcd for $C_{10}H_{10}F_3NO$: C, 55.29; H, 4.64; N, 6.44. Found: C, 55.54; H, 4.83; N, 6.36.

(*R*)-(+)-N-Methyl-α-trifluoromethylphenylthionacetamide [(*R*)-(+)-N-Methyl-2-phenyl-3,3,3-trifluoropropanthionamide].—A mixture of 496 mg of (*S*)-(+)-N-methyl-2-phenyl-3,3,3-trifluoropropionamide, $[\alpha]^{23}D$ +33.8 ($CHCl_3$), 272 mg of sulfurated potash (Allied Chemical Co.), 337 mg of phosphorus pentasulfide (Matheson Coleman and Bell), and 10 ml of *m*-xylene was protected with a condenser and drying tube and was heated over a period of 30 min to 140°. The temperature was maintained at this value for one hr. After slight cooling the supernatant liquid was filtered, and the residue was reheated with 10 ml of *m*-xylene for 30 min. This solution was

filtered and the combined filtrates were reduced to dryness under reduced pressure. The residue was dissolved in hot benzene and was filtered to remove sulfur. The filtrate was chromatographed on 20 g of silica gel, 60–200 mesh (Davison Chemical Co.). Elution with benzene removed sulfur readily and subsequent elution with 3:1 benzene–ethyl acetate removed 274 mg of a slightly yellow oil. This material was evaporatively distilled at a bath temperature of 120°, 0.1 mm. The product obtained was 150 mg (28%) of yellow oil: $[\alpha]^{22}D$ −5.4 ± 1.3 (*c* 1.49, $CHCl_3$); infrared bands 3275, 1540, 1120, and 1160 cm^{-1}. In methanol the material was dextrorotatory at the sodium D line. The ORD data are reported in Table III.

Anal. Calcd for $C_{10}H_{10}F_3NO$: C, 51.49; H, 4.32; N, 6.00. Found: C, 51.40; H, 4.39; N, 6.17.

N-Methyl-α-ethyl-*p*-methoxyphenylthionacetamide (N-Methyl-2-*p*-methoxyphenylbutanthionamide).—The acid chloride, prepared from thionyl chloride and α-ethyl-*p*-methoxyphenylacetic acid, 1.0 g, $[\alpha]^{20}D$ +5.36, enantiomorphic purity 8.5%, was treated with 40% aqueous methylamine, 2 ml and the amide was isolated by washing the benzene layer successively with water, sodium bicarbonate solution, and saturated salt solution. The benzene layer was dried ($MgSO_4$) and evaporated to dryness, and the residue was recrystallized from petroleum ether (bp 77–110°) to give a product, 0.90 g, mp 97–100°, $[\alpha]^{20}D$ +3.3 ± 0.5 (EtOH), *c* 2). Since the yield of this material is 78%, the enantiomorphic purity must be 8.5 ± 2%.

This N-methylamide, 507 mg, was treated with sulfurated potash, 302 mg, and phosphorus pentasulfide, 363 mg, in xylene, 10 ml, by heating to 70–80° over a 15-min period and holding the temperature at this value for 60 min. The soluble portion was decanted and the residue was heated with a fresh portion of xylene at 110° for 30 min. The xylene mixture was filtered, and the filtrate was combined with the previous xylene solution and evaporated to dryness to give 546 mg of a mixture of oil and solid. Since this contained a small band in the infrared spectrum at 1625 cm^{-1} indicative of unreacted amide, this crude product was again treated with sulfurated potash, 200 mg, and phosphorus pentasulfide, 245 mg, in xylene at 100° for 45 min. Isolation as before, followed by chromotography on silica gel, gave an oil which was further purified by evaporative distillation at 160° (1 mm) to give 203 mg (38% yield). The infrared spectrum of this material was essentially identical with that of the crude initial product and the second reaction period may not have been necessary. The ORD data are reported in Table III.

(*S*)-(+)-α-Ethyl-*p*-methoxyphenylacetamide [(*S*)-(+)-2-*p*-Methoxyphenylbutanamide].—Ethyl-*p*-methoxyphenylacetic acid, $[\alpha]^{30}D$ +63.25, 0.850 g, was refluxed with thionyl chloride, 2 ml, for 1 hr and the excess thionyl chloride was thoroughly removed under reduced pressure. The residue was dissolved in benzene, 10 ml, and into half of this solution was bubbled anhydrous ammonia. The precipitate was removed by filtration and digested with hot benzene; the combined benzene extracts were concentrated to dryness. The residue, 4.2 g, was twice recrystallized from petroleum ether (bp 60–80°) to give a product mp 111–113°, $[\alpha]^{24}D$ +23.0 ± 0.8 (absolute ethanol, *c* 1).

Anal. Calcd for $C_{11}H_{15}NO_2$: C, 68.37; H, 7.82. Found: C, 68.16; H, 7.83.

(*S*)-(+)-α-Ethyl-*p*-methoxyphenylacetanilide [(*S*)-(+)-2-*p*-Methoxyphenylbutananilide].—To the other half of the above benzene solution of the acid chloride was added 0.4 ml of aniline. Upon cooling the solution was filtered and the precipitate of aniline hydrochloride extracted with warm petroleum ether. The solution was evaporated to dryness (1 mm, 80°) and the residue was twice crystallized from petroleum ether (bp 60–80°) to give the purified anilide, 0.33 g, mp 125–127°, $[\alpha]^{24}D$ +80.0 ± 0.8 (absolute ethanol, *c* 2.75).

Anal. Calcd for $C_{17}H_{19}O_2N$: C, 75.81; H, 7.11. Found: C, 75.76; H, 7.10.

Registry No.—α-Trifluoromethylphenylacetaldehyde 2,4-DNPH, 13491-12-8; (−)-α-isopropylphenylacetic acid, 13491-13-9; α-isopropylphenylacetic acid cinchonidene salt, 13491-14-0; (−)-α-*t*-butylphenylacetic acid, 13491-16-2; (−)-α-trifluoromethylphenylacetic acid (+)-α-phenylethylamine salt, 13491-15-1; (−)-α-trifluoromethylphenylacetic acid, 13491-17-3; α-ethyl-*p*-methoxyphenylacetic acid cinchonidine salt, 13491-18-4.

Infrared Frequency Shifts of Phenol Owing to Hydrogen Bonding with Substituted Aromatics[1,2]

EIJI ŌSAWA, TOKINOBU KATŌ, AND ZEN-ICHI YOSHIDA

Department of Synthetic Chemistry, Faculty of Engineering, Kyoto University, Yoshida, Kyoto, Japan

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The frequency shifts $\Delta\nu_{OH}$ of phenol owing to hydrogen bonding with the ring π electrons of a number of mono- and polysubstituted benzenes and naphthalenes relate linearly with $\Sigma(\sigma_m + \sigma_p)/2$, rather than with $\Sigma\sigma_p$, suggesting a random orientation of the weak complex between phenol and π bases. The $\Delta\nu$ *vs.* $\Sigma(\sigma_m + \sigma_p)/2$ relation is not disturbed even when aromatic bases like hexaethylbenzene are used, so that it offers a simple method of estimating approximate $\sigma_m + \sigma_p$ values of the alkyl substituents. N-alkylanilines and 2,6-di-*t*-butylphenols were found to act solely as π bases in dilute carbon tetrachloride solution.

It has often been observed that aryl ethers[3,4] and N,N-dimethylaniline[4,5] act as the bifunctional proton acceptors in hydrogen bonding. The two donor sites have been estimated to be the ring π electrons and the lone-pair electron on oxygen or nitrogen atom. Recently, Wayland and Drago[6] confirmed this assignment by demonstrating, for the adducts between phenol and a number of monosubstituted benzenes in CCl_4 solutions, two linear relations between $\Delta\nu_{OH}$ (π) of phenol and σ_p of the substituent on the benzene ring and between $\Delta\nu_{OH}$ (n) and $\Sigma\sigma^*$ of substituents bonded to O or S atoms.

In view of the abundant evidence[1,2,7,8] that X–H group lies near the center of the benzene ring with a certain degree of the thermal movement in the π-hydrogen bond complex, the use of σ_p constants in one of the Wayland–Drago relations ($\Delta\nu_{OH}$ (π) *vs.* σ_p) does not seem to be the best choice, since it implies the localization of phenol on the *para* or *ortho* carbon of the

(1) Part III of the series Intermolecular Hydrogen Bond Involving a π-Base as the Proton Acceptor.

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(5) L. J. Bellamy and R. L. Williams, *Proc. Roy. Soc.* (London), **A254**, 119 (1960). In these papers the proton acceptors were used as the solvents.

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