by rotary evaporation left the crude product as an oil, which was dissolved in a few milliliters of hot MeOH and after the addition of EtCOMe the pure dihydrochloride of Ib [1.63 g; 70%; mp 186° (lit.[36] 184°)] separated out. Ic was prepared as follows. The dihydrochloride of Ib (0.42 g) was suspended in Et_2O (50 ml) containing 2 drops of H_2O and after the addition of one pellet of NaOH the mixture, contained in a mortar, was vigorously triturated with a pestle. In this way, the free base of the substrate passed into the Et_2O and NaCl solid began to appear. The ethereal solution was decanted off and dried (Na_2SO_4), and MeI (0.15 ml) was added to the filtered solution. After a few minutes the quaternary methiodide began to separate. After standing at 0°, several collections yielded Ic (0.22 g, 40%), mp 236° (MeOH-Et_2O). *Anal.* ($C_8H_{16}IN_3$) C, H. Samples were dissolved in D_2O and spectra were recorded on Varian A-60 and HA-100 spectrometers, using *tert*-butyl alcohol as internal reference. These chemical shifts were then referred to TMS by the addition of 1.26 ppm. The pH values were determined with a glass electrode and are not corrected to pD values. Generally the line widths were found to be pH dependent and the pH of the solution was adjusted by adding NaOD to give the best line width within the pH region of interest.

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A New Chiral Reagent for the Determination of Enantiomeric Purity and Absolute Configuration† of Certain Substituted β-Arylethylamines

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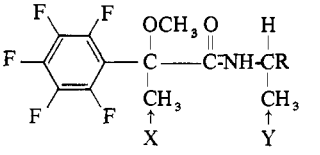
The synthesis and resolution of α-methyl-α-methoxypentafluorophenylacetic acid are described. The resolved acid has electron-capture properties and is shown to be a useful reagent for the determination of enantiomeric composition of chiral arylethylamines by glc after exposure of racemic amines to biological membranes. It is also shown to be a useful reagent for the prediction of the absolute configuration of certain substituted β-arylethylamines by nmr.

The determination of the enantiomeric composition of chiral substances in recent years has been the subject of considerable investigation both in chemistry and biology. The methods most commonly employed in these studies have been based either on glc or nmr. Early workers[2] demonstrated the utility of glc as a method of estimating enantiomeric composition and the same fundamental approach was utilized by Raban and Mislow,[3a,‡] who showed that enantiomeric composition could also be determined by nmr after conversion to a diastereomeric mixture. Dale, Dull, and Mosher[4a] refined the nmr method by developing the chiral reagent α-methoxy-

†A preliminary report of this work was presented at the 162nd National Meeting of the American Chemical Society and a short description has appeared (ref 1). This investigation was supported in part by NIH Training Grant No. 5-TO1-GM00728 and in part by a Mead Johnson Laboratories Undergraduate Research Award, 1968–1969. We would like to express our gratitude to Drs. S. Matin, M. Rowland, and N. Castagnoli for a gift of the amines of unknown absolute configuration and for their help and consultation in the work involving electron capture glc. In addition, we would like to express our gratitude to Messrs. Forland and Wolfe and Dr. L. Z. Benet for their help and consultation in the rat intestinal experiment.

‡For a critical review of the nmr method, see ref 3b.

Table I. A Correlation of the Nmr Chemical Shifts and Glc Retention Times of a Series of Amides to the Absolute Configuration of Their Constituent Arylphenethylamines



Amine, R =	Configuration and/or sign of rotation	Chemical shift of diastereomers of (+)-1 in ppm downfield from TMS: α-Methyl (acid, X)	α-Methyl (amine, Y)	Retention time, min[a]	Predicted absolute configuration
Ph-	*S* (−)	1.65	1.28	3.5	
	R (+)	1.75	1.22	3.3	
α-Naphthyl-	*S* (−)	1.68	1.50	22.0	
	R (+)	1.78	1.35	18.0	
$PhCH_2$-	*S* (+)	1.65	0.98	12.5	
	R (−)	1.75	0.90	12.0	
3,4,5-Trimethoxy-$PhCH_2$-	(+)	1.67	1.05	29.5	*S*
	(−)	1.78	0.97	27.5	*R*
2,3,5-Trimethoxy-$PhCH_2$-	(+)	1.63	1.22	26.0	*S*
	(−)	1.80	1.15	22.5	*R*
2,5-Dimethoxy-4-methyl-$PhCH_2$-	(+)	1.60	1.22	17.5	*S*
	(−)	1.78	1.15	15.2	*R*

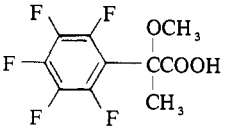
[a] Glc analyses run on Varian 2100, 3% SE-30, Varaport 30, 100–120, 5 ft × 0.25 in. × 2 mm (i.d.), N_2 40 ml/min, H_2 30 ml/min, air 300 ml/min, injection 225°, detection 245°, column 190°, except for amphetamine amides where a column temperature of 170° was used.

α-trifluoromethylphenylacetyl chloride, while Hoyer, *et al.*,[4b] have utilized chemical shift differences and relative retention times as an indication of the absolute configuration of diastereomeric amides produced by coupling of *d*-camphor-10-sulfonic acid to a series of chiral amines. An elegant variation of the same theme was provided by Pirkle and Beare who employed chiral solvents to determine both the enantiomeric composition and absolute configuration of alkylarylcarbinols,[5] α-arylethylamines,[6] α-hydroxy acids,[7] sulfoxides,[8] and α-amino acids.[9]

A recent advance in glc analysis has been the utilization of derivatizing agents having electron capture (ec) properties.§ This has allowed both the qualitative and quantitative analysis of substances from biological fluids at levels never achieved before. A refinement of this technique important to drug research would be the application of a chiral reagent having good ec properties to study the influence of distribution, metabolism, and elimination on the enantiomeric composition of chiral drugs from body fluids.

Our attention was thus directed toward the development of a single derivatizing agent that might be useful for the determination of absolute configuration within a homologous series and enantiomeric composition by both nmr and glc. To achieve this end we have synthesized and resolved α-methyl-α-methoxypentafluorophenylacetic acid (**1**). The substance lacks an α hydrogen and thus is resistant to racemization. For nmr analysis it contains groups which are easily analyzed and display chemical shift changes with changes in configuration. For glc analysis the substance is volatile and contains a pentafluorophenyl group which confers on it good ec properties.

Synthesis of 1. *rac*-**1** was synthesized by bisulfite addition to pentafluorobenzaldehyde, followed by cyanide addition and acid hydrolysis, to give pentafluoromandelic acid (**2**),



which was then esterified with diazomethane to give its methyl ester **3**, followed by oxidation with *N*-bromosuccinimide to the α-keto ester **4**. The α-keto ester **4** was allowed to react with methylmagnesium bromide to give the α-hydroxy-α-methyl ester **5**, followed by methylation with methyl iodide and silver oxide to give the methyl ether **6**. Acid hydrolysis of **6** gave *rac*-**1**. *rac*-**1** was resolved *via* crystallization of the quinine salts to give (+)- and (−)-**1**. The (+) enantiomer was found to be nearly 100% enantiomerically pure as indicated by a glc analysis of an amide mixture made from enantiomerically pure α-phenylethylamine and was therefore used in our studies.

Since, to our knowledge, little work had been done on the stereochemistry and pharmacodynamics of the enantiomers of various amphetamine analogs, we began a study in this series of compounds by applying **1** to six representative arylethylamines (Table I). The chiral acid **1** was first reacted with *N,N'*-carbonyldimidazole to give an activated imidazolide, which was then allowed to react with the amines to give the diastereomeric amides.

Nmr Results. The nmr spectrum of the diastereomeric amides **7**, derived from the (+) isomer of **1**, and (*R*)- and (*S*)-α-phenylethylamine (Figure 1a) is typical of the spectra that we have observed. In this spectrum the two diastereomeric amides can be discerned from the overlapping doublets of the diastereotopic# α-methyl group of the amine moiety and from the overlapping triplets of the diastereotopic α-methyl group of the acid moiety. The triplet signal is the result of long-range coupling with the *o*-fluoro groups, J_{FH} = 3.5 Hz, and has been confirmed by measurement of the spectrum at

§ The use of electron-capture (ec) achiral derivatizing agents (for a review of electron attachment mechanisms, see ref 10, and for a theoretical proposal for the basis of the electron-capture sensitivity of several ec derivatizing agents, see ref 11) has proven to be extremely useful for the qualitative and quantitative analysis of melatonin,[12] chlordiazepoxide,[13] estrogens,[14] and biogenic amines[15] in biological fluids, at levels that cannot be detected by the flame ionization detector. Moffat,[16] Wilkinson,[17] and Matin[11] have studied several ec derivatizing agents and have demonstrated that pentafluorobenzaldehyde and pentafluorobenzoyl chloride could be used to detect amines in biological fluids at the 10-pg level. Thus, to confer volatility and good ec properties on our chiral reagent, we chose a pentafluorophenyl group.

Enantiotopic and diastereotopic are terms used by Mislow and Raban.[18] Diastereotopic groups are defined as those groups which exist in a diastereomeric environment and as a consequence may exhibit different chemical shifts when two diastereoisomers are compared.

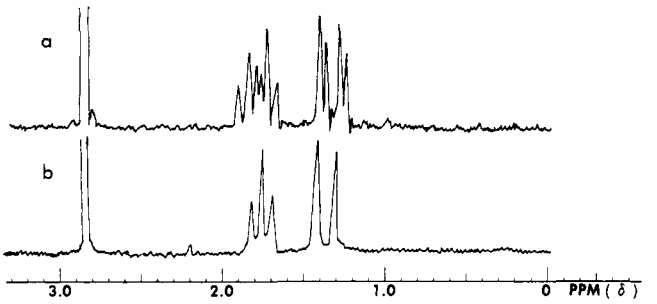


Figure 1. (a) Nmr spectrum of the diastereomeric amides derived from the (+) isomer of 1 and (*R*)-(+)- and (*S*)-(−)-α-phenylethylamine. (b) Nmr spectrum of the diastereomeric amide derived from the (+) isomer of 1 and (*S*)-(−)-α-phenylethylamine.

60 and 100 MHz. Benzene was chosen as the nmr solvent, since it accentuated these diastereotopic differences. In the nmr spectrum of the diastereomeric amide 8, derived from (*S*)-α-phenylethylamine (Figure 1b), it can be seen that the doublet from the α-methyl group of the amine moiety corresponds to the downfield doublet in the mixture of diastereomeric amides (Figure 1a), while the triplet from the α-methyl group of the acid moiety corresponds to the upfield triplet in the mixture of diastereomeric amides (Figure 1a). Thus, it follows that the upfield doublet and the downfield triplet, in the diastereomeric mixture (Figure 1a), correspond to the amide derived from (*R*)-α-phenylethylamine. The same pattern was observed when the diastereomeric amides of α-naphthylethylamine (9) and amphetamine (11) were studied; *i.e.*, both compounds having the *R* absolute configuration in the amine moiety gave upfield doublets and downfield triplets with respect to their corresponding diastereomers (Table I). The diastereomeric amides of the three amines of unknown absolute configuration, 3,4,5-trimethoxyamphetamine (13), 2,4,5-trimethoxyamphetamine (14), and 2,5-dimethoxy-4-methylamphetamine (15), display similar sets of a downfield doublet coupled with an upfield triplet or an upfield doublet coupled with a downfield triplet (Table I). These differences arise from the intrinsic chirality of the molecule and are due to the spatial arrangement of the substituent groups at an asymmetric center with respect to each other. It therefore seems unlikely that a complete reversal of a chemical shift trend would occur within a homologous series particularly if the substituent changes are minor in comparing one homolog with the next. Hence, it seems reasonable to tentatively assign the *R* absolute configuration to amides 13, 14, and 15 which give an upfield doublet and a downfield triplet (Table I).

Glc Results. The glc retention times of the diastereomeric amides are also presented in Table I. The amides derived from the amines of known *R* absolute configuration have shorter retention times than the amides derived from their respective enantiomers having the *S* configuration. Similarly, the amides derived from those amines tentatively assigned the *R* configuration on the basis of nmr also have shorter retention times than the amides derived from their respective enantiomers. Hence, a consistent pattern is observed in both the nmr and glc data; *i.e.*, the absolute configurational assignments based upon the nmr results agree with the predictions based upon the glc results (Table I). Moreover, these predictions have recently been supported by glc retention time and ORD studies reported by Matin and Castagnoli.[19,**]

**S. Matin and N. Castagnoli, private communication.

One of the goals that initiated this study was to develop a chiral reagent that would have good ec properties. Moffat, Wilkinson, and Matin[§] have studied several ec derivatizing agents and have concluded that generally the pentafluorophenyl group confers a high degree of ec ability to a molecule in which it is incorporated. Consistent with their results we have found that the amide formed from α-phenethylamine and 1 was detectable at the 300-pg level, 5% full-scale deflection at an attenuation of 1 × 8 with insignificant noise. The other amides reported in this investigation were not studied but presumably the limit of their detectability would be of the same order of magnitude.

Preliminary Biological Studies. The study of the absorption, distribution, metabolism, and excretion of enantiomers is usually done separately. Superficially, it would seem advantageous to administer a racemic mixture and assay for the individual enantiomers and their metabolities, since the biological variation is controlled and thus fewer animals or tissue preparations are needed. However, both studies should be done; otherwise competitive inhibition effects of one enantiomer on the other in routes of metabolism, etc., may be missed. In order to undertake an experiment of the latter kind, one must have a method of distinguishing the enantiomers. To this end we have employed 1 in two test systems, that of buccal absorption and intestinal absorption.

Buccal Absorption. Beckett and Triggs[20] have studied the buccal absorption of the enantiomers of several amine drugs and have found no difference in the amount of enantiomers absorbed during a period of 5 min. We found their results somewhat perplexing because membranes are chiral structures and *a priori* one might expect the rate of transfer of the enantiomers of another substance through such a structure to be different because of dissymmetric interactions during the course of passage. Using their basic experimental procedure, we examined the buccal absorption of racemic α-phenethylamine hydrochloride. A solution of the drug was placed in the mouth, swirled for 5 min, and expelled, and the residual material was allowed to react with the imidizolide of (+)-1. The resulting mixture was then analyzed by glc to determine enantiomeric composition. Since the peaks, due to the diastereomers, were found to be of equal area, it appeared that under our experimental conditions and in agreement with Beckett and Triggs findings the enantiomers had been equally absorbed.

Intestinal Absorption. Pursuing the idea that biological membranes are chiral structures and should therefore differentiate between enantiomeric substances passing through them, we studied the absorption of racemic α-phenethylamine through the everted rat intestine. The method we used was that of Forland, Wolfe, and Benet. (See ref 21. Several references dealing with the transport of drugs across intestinal membranes are presented in this paper.) The unstripped everted intestine was placed into a buffered solution of racemic α-phenylethylamine and samples were taken from the inner compartment after 5, 15, 30, and 45 min and allowed to react with the imidazolide of (+)-1. The resulting diastereomeric amides were then analyzed by glc. Both (*R*)- and (*S*)-α-phenylethylamine appeared to pass through the intestinal membrane at the same rate, since the peak areas of the diastereomeric amides were identical after each sampling.

Discussion

The acid 1 has been shown to be a useful chiral derivatizing agent. Its major advantages over presently available agents are that it can be used for both nmr and glc studies of enantio-

meric composition and possibly absolute configuration in a series of β-arylethylamines. In addition, it is resistant to racemization and has good ec properties.

Preliminary studies on the buccal and intestinal absorption of α-phenylethylamine indicate that there is no detectable discrimination between the two enantiomers. Whether this is an isolated case or a general phenomenon remains to be determined. However, the results raise questions as to the mechanism of membrane absorption. Do small drug molecules actually penetrate the membrane, in which case differences in the rate of enantiomeric passage would be expected to be different, or do they channel through spaces or holes within the membrane network, in which case differences would be expected to be minimal? The answer to these questions awaits further experimentation.

Experimental Section

Melting points were taken on a Thomas-Hoover melting point apparatus, nmr spectra on a Varian A-60 instrument, ir on a 338 Perkin-Elmer instrument, glc on a Varian 2100 instrument, and mass spectra on an AEI MS-902 high-resolution mass spectrometer.

2,3,4,5,6-Pentafluoromandelic Acid (2). Compound **2** has been prepared by a similar method.[22] Pentafluorobenzaldehyde, 100 g (0.51 mol, Pierce Chemical), was added slowly (0.5 hr) with mixing to a saturated solution of $NaHSO_3$, 530 g (5.1 mol), in 884 ml of H_2O. After 15 and 45 min of stirring, absolute EtOH (10 ml) was added to the reaction mixture. After 3 hr the viscous white suspension was filtered and washed several times with Et_2O. An ice-cooled solution of NaCN, 36 g (0.74 mol), in 180 ml of H_2O was added slowly (30 min) with stirring to a cooled solution (10–11°) of the above white material (dissolved in 1200 ml of H_2O). The resulting white suspension was stirred at room temperature for 12 hr, yielding a yellow suspension, which was then filtered. The filtrate was extracted several times with Et_2O, and the Et_2O extract was then combined with an ethereal solution of the precipitate, extracted (H_2O), and vacuum evaporated to yield a yellow solid. The yellow solid was then hydrolyzed by refluxing (10 hr) with 600 ml of concentrated HCl, extracted (Et_2O), back-extracted into a $NaHCO_3$ solution, which was further extracted (Et_2O), acidified (concentrated HCl), and then extracted (Et_2O). The Et_2O extract was washed (H_2O), dried ($MgSO_4$), and vacuum evaporated to give a yellow solid which was recrystallized (C_6H_6) to yield 2: 67 g (54%); white crystals; mp 143–145° (lit.[22] mp 141–142°); ir (Nujol, cm^{-1}) 3420, 1765, 1670, 1550, 1530, 1135, 1085, 1005, 985, 910, 810, 680.

Methyl Pentafluoromandelate (3). Compound **2**, 67 g (0.27 mol), was dissolved in 150 ml of anhydrous Et_2O, and the resulting solution was cooled in an ice bath. Diazomethane was generated from Diazald (100 g, 0.47 mol, Aldrich) in the usual manner and delivered with stirring into the cooled solution of 2. The resulting yellow solution was stirred for an additional 4.5 hr at 0° and then vacuum evaporated to give a light green solid which was recrystallized (hexane) to yield 3: 66.3 g (96%); white crystals; mp 62–64°; ir (Nujol mull, cm^{-1}) 3370, 1770, 1765, 1660, 1540, 1520, 1000, 950, 760; nmr (60 MHz, $CDCl_3$) δ (ppm) 5.35–5.55 (broad, 1 H), 3.80 (s, 3 H), 3.50–3.70 (broad, 1 H, exchanges with D_2O). *Anal.* ($C_9H_5O_3F_5$) C, H.

Methyl Pentafluorophenylglyoxylate (4). Compound **3**, 66.3 g (0.26 mol), and NBS, 84 g (0.47 mol), in 1000 ml of CCl_4 was refluxed with stirring for 68 hr. The resulting red-orange suspension was filtered, and the filtrate was vacuum evaporated to yield a yellow oil. Distillation gave pure 4: 58 g (88%); bp 62–66° (0.2 mm); ir (neat, cm^{-1}) 3020, 2970, 1780, 1770, 1670, 1545, 1520, 1460, 1440, 1350, 1000, 790; nmr (60 MHz, $CDCl_3$) δ (ppm) 4.0 (s). *Anal.* ($C_9H_3O_3F_5$) C, H.

Methyl α-Hydroxy-α-methylpentafluorophenylacetate (**5**). Compound **4**, 54 g (0.21 mol), in 530 ml of anhydrous Et_2O (Na dried), under N_2, was cooled to −6° in an ice-salt bath. MeMgBr (0.25 mol, 85 ml of a 3 *M* in Et_2O solution, Alfa Inorganics) and 150 ml of anhydrous ether were mixed and added slowly (1.5 hr) with stirring to the Et_2O solution of **4**. The resulting light-yellow suspension was stirred an additional 2.5 hr at −6 to 0°, hydrolyzed with 100 ml of 6 *N* HCl, and then extracted with Et_2O. The combined Et_2O extracts were washed (H_2O), dried ($MgSO_4$), and vacuum evaporated to give a yellow viscous oil. Distillation gave **5**: 48 g (85%); bp 73–76° (0.8 mm); ir (neat, cm^{-1}), 3500, 3010, 2970, 1765, 1665, 1540, 1510, 1470, 990, 710; nmr (60 MHz, $CDCl_3$) δ (ppm) 4.0–4.3 (broad, 1 H), 3.82 (s, 3 H), 1.90 (t, 3 H, J = 2 Hz, coupled with *o*-fluorines). *Anal.* ($C_{10}H_7O_3F_5$) C, H.

Methyl α-Methoxy-α-methylpentafluorophenylacetate (**6**). Compound **5**, 46 g (0.17 mol), silver oxide, 80 g (0.34 mol), and MeI, 900 g (6.3 mol), were refluxed with stirring. After 40 hr an additional 30 g (0.13 mol) of Ag_2O was added to the reaction mixture, which was then refluxed for an additional 30 hr. The reaction mixture was then filtered and vacuum evaporated to give a viscous yellow oil. Distillation gave **6**: 46.5 g (96%); bp 74–77° (0.3 mm); ir (neat, cm^{-1}) 3000, 2960, 2840, 1765, 1670, 1540, 1510, 1470, 1390, 990, 780; nmr (60 MHz, $CDCl_3$) δ (ppm) 3.82 (s, 3 H), 3.32 (s, 3 H), 1.90 (t, 3 H, J = 2 Hz). *Anal.* ($C_{11}H_9O_3F_5$) C, H.

α-Methoxy-α-methylpentafluorophenylacetic Acid (**1**). Compound **6**, 40 g (0.14 mol), concentrated HCl (160 ml), H_2O (300 ml), and dioxane (840 ml) were refluxed for 86 hr. The reddish-brown reaction mixture was vacuum evaporated to give an oil which was dissolved in ether and extracted with Na_2CO_3. The Na_2CO_3 extract was acidified (HCl), washed (H_2O), dried ($MgSO_4$), and vacuum evaporated to yield the oil (1): 35 g (92%); ir (neat, cm^{-1}), 3700–3050 (broad), 2950, 2840, 1760, 1660, 1540, 1510, 1470, 1320, 985, 810; nmr (60 MHz, $CDCl_3$) δ (ppm) 10.33 (s, 1 H), 3.32 (s, 3 H), 1.97 (t, 3 H, J = 2 Hz); mass spectrum m/e 270. An analysis was not run on the racemic acid but was run on its quinine salt. *Anal.* ($C_{30}H_{31}O_5N_2F_5$) C, H, N.

Base hydrolysis of **6** was originally attempted but proved to give a mixture of products which, on the basis of mass spectral evidence, was composed of predominantly a monohydroxylated tetrafluorophenyl derivative. This compound apparently was formed by aromatic nucleophilic substitution but was not characterized further. Moffat[16c] has observed similar reactions when pentafluorobenzaldehyde was condensed with secondary amines.

Resolution of *rac*-**1**. *rac*-**1**, 35 g (0.13 mol), quinine, 42 g (0.13 mol), and a 1:1 mixture of hexane and Me_2CO (200 ml) were mixed, and resulting salt was dissolved by boiling the mixture and recrystallizing by slowing cooling the hot solution to room temperature. The salt was filtered, washed with a minimum of cold hexane–acetone (1:1), and recrystallized several more times to give a white crystalline (needle) salt: mp 203–204°; 12.3 g; $[\alpha]^{22}D$ −118° (*c* 3.00, EtOH). A small amount of the salt was decomposed with dilute HCl, and the regenerated acid was extracted (ether), dried ($MgSO_4$), and vacuum evaporated to give a colorless, viscous oil, $[\alpha]^{22}D$ −34° (*c* 3.44, MeOH). During the reprocessing of the solids from the initial filtrates, another salt was collected: white powder; 12.9 g; mp 173–174°; $[\alpha]^{22}D$ −82° (*c* 3.00, EtOH). It was decomposed to give a colorless, viscous oil, $[\alpha]^{22}D$ +44° (*c* 3.27, MeOH). Both enantiomers gave the same nmr and ir spectra as the racemic acid.

Preparation of Amides for Nmr and Glc Absolute Configuration Studies. Two syntheses were carried out for each amine. The initial synthesis was with (+)-1 and racemic amine to give a diastereomeric mixture which was analyzed by nmr and glc. The second synthesis was with (+)-1 and resolved or partially resolved amine to yield a single diastereomer (or an enriched diastereomeric mixture in the case of the substituted amphetamines) which was analyzed by nmr and glc in order to determine where it corresponded in the nmr spectrum and glc chromatogram of the diastereomeric mixture. The other diastereomer in the nmr spectrum and glc chromatogram would correspond to the amide derived from the other enantiomeric amine. The preparation of *N*-α-phenylethyl-α-methoxy-α-methylpentafluorophenylacetamide (7) will illustrate the procedure used for the synthesis of the amides.

N-α-Phenylethyl-α-methoxy-α-methylpentafluorophenylacetamide (**7**). Compound (+)-(**1**), 140 mg (0.52 mmol), dissolved in 5 ml of anhydrous THF and *N,N'*-carbonyldiimidizole, 100 mg (0.62 mmol, dissolved in 5 ml of anhydrous THF), were combined and the resulting solution was stirred at room temperature for 19 hr. Racemic α-phenylethylamine, 65 mg (0.52 mmol, in 1 ml of anhydrous THF), was added to the colorless reaction solution and stirred for an additional 19 hr at room temperature. The resulting colorless reaction solution was vacuum evaporated to give a crystalline residue, which was dissolved in Et_2O, extracted (HCl, $NaHCO_3$, H_2O), dried ($MgSO_4$), and vacuum evaporated to give a white solid: 150 mg (77%); mp 79–107°; ir (KBr pellet, cm^{-1}) 3420, 2970, 1690, 1530, 1500, 1390, 1320, 1170, 1080, 980, 850, 710, 560; mass spectrum m/e 373.

N-(S)-α-Phenylethyl-(+)-α-methoxy-α-methylpentafluorophenylacetamide (**8**): mp 111–112° (recrystallized from hexane–C_6H_6); ir (same as diastereomer mixture). *Anal.* ($C_{18}H_{16}O_2N_1F_5$) C, H, N.

N-α-Naphthylethyl-(+)-α-methoxy-α-methylpentafluorophenylacetamide (**9**): mp 107–138°; ir (KBr pellet, cm^{-1}) 3420, 3300, 2950, 1680, 1540, 1500, 1380, 1320, 1165, 1080, 980, 780, 560.

N-(S)-α-Naphthylethyl-(+)-α-methoxy-α-methylpentafluorophenylacetamide (**10**): mp 148–149° (recrystallized from hexane–C_6H_6); ir (same as diastereomer mixture). *Anal.* ($C_{22}H_{18}O_2N_1F_5$) C, H, N.

N-α-Methylphenylethyl-(+)-α-methoxy-α-methylpentafluorophen-

ylacetamide (11): oil; ir (neat, cm^{-1}) 3410, 3320, 2920, 1670, 1520, 1490, 1375, 1310, 1150, 1080, 980, 830, 700, 550.

N-(S)-α-**Methylphenylethyl-(+)**-α-**methoxy**-α-**methylpentafluoro**-**phenylacetamide (12)**: oil; purified by glc; ir (same as diastereomer mixture). *Anal.* ($C_{19}H_{18}O_2N_1F_5$) C, H, N.

N-α-**Methyl-3,4,5-trimethoxyphenylethyl-(+)**-α-**methoxy**-α-**methyl**-**pentafluorophenylacetamide** (13): oil; ir (neat, cm^{-1}) 3400, 3350, 2950, 1700, 1530, 1500, 1470, 1390, 1240, 1080, 980, 830, 710, 560; nmr consistent with structure. Diastereomers were not completely separated or submitted for analysis.

N-α-**Methyl-2,4,5-trimethoxyphenylethyl-(+)**-α-**methoxy**-α-**methyl**-**pentafluorophenylacetamide** (14): oil; ir (neat, cm^{-1}) 3400, 2950, 1690, 1520, 1480, 1380, 1320, 1260, 1080, 980, 840, 710, 690; nmr consistent with structure. Diastereomers were not completely separated or submitted for analysis.

N-α-**Methyl-2,5-dimethoxy-4-methylphenylethyl-(+)**-α-**methoxy**-α-**methylpentafluorophenylacetamide (15)**: oil; ir (neat, cm^{-1}) 3400, 3360, 2960, 1690, 1530, 1500, 1480, 1390, 1250, 1080, 980, 840, 710; nmr consistent with structure. Diastereomers were not completely separated or submitted for analysis.

Buccal Absorption Study. Racemic α-phenylethylamine hydrochloride, 2.5 mg (0.016 mmol), was dissolved in 1 ml of H_2O and was then diluted with 25 ml of isotonic phosphate buffer, pH 8.0. The resulting solution was placed into the mouth, swirled vigorously for 5 min, and was then expelled. The mouth was then washed with 10 ml of H_2O and the washing was added to the expelled buffer solution, which was then basified with 1 ml of 1 *N* NaOH, extracted (ether, 25 ml), dried ($MgSO_4$), evaporated (N_2), and then allowed to react with 1 ml (0.05 mmol) of the (+)-**1** imidazolide solution (0.05 mmol/ml) for 1 hr at room temperature. The resulting solution was then directly chromatographed on a Varian 2100 gas-chromatograph flame detector, 3% SE-30, varaport 30 100–120, 5 ft × 0.25 in. × 2 mm (i.d.), injection 230°, detection 250°, column 147°, N_2 40 ml/min, H_2 30 ml/min, air 300 ml/min. A control was prepared by repeating the above procedure except that the 2.5 mg of amine HCl was added after the buffer solution was expelled from the mouth. This was done in order to ensure that a racemic mixture would analyze as two diastereomeric amides of equal peak area.

Rat Everted Intestine Study. A male Sprague–Dawley rat weighing approximately 300 g was allowed free access to both food and water prior to the experiment. The rat was sacrificed by a sharp blow at the base of the skull. The small intestine was exposed *via* a midline abdominal incision, and the gut was then wetted with Krebs bicarbonate buffer, pH 7.4. The first 25 cm of the intestine distill to the pylorus was discarded and the next 30 cm of the intestine was flushed with approximately 20 ml of Krebs bicarbonate buffer, pH 7.4. Four to six 0.5-cm sections were cut from the washed 30-cm section, were slid onto a glass rod with a tapered point that had been prewetted in buffer, and were then everted upon the rod. One end of the everted intestine segment was fastened to the tapered end of a reservoir tube with 3-0 surgical silk, while the other end was tied off with a piece of silk to form a sack that was 5 cm in length. The reservoir of each intestine preparation was filled with 3 ml of phosphate buffer, pH 7.4 (37°), immersed in 15 ml of phosphate buffer, pH 7.4 (37°), which contained 1 mg/ml of racemic α-phenylethylamine hydrochloride, and was aeriated with a mixture of 95% O_2–5% CO_2. The entire apparatus was then placed into a constant temperature bath (37°). A picture of the apparatus is given in Forland, Wolfe, and Benet's paper.[21]

A sample, 1–2.5 ml, was taken from each intestine reservoir. Intervals of 5, 15, 30, and 45 min were used. NaOH (1 *N*, 0.5 ml) was added to each sample and each sample was extracted twice with Et_2O (3 ml), dried ($CaCl_2$), evaporated (N_2), and then allowed to react with the (+)-imidazolide solution of **1**, 0.1 ml (0.005 mmol), for 1 hr at room temperature. The resulting solutions were then directly chromatographed utilizing the same conditions used in the buccal absorption study.

Electron-Capture Sensitivity of *N*-α-Phenylethyl-α-methoxy-α-**methylpentafluorophenylacetamide (7)**. A Varian 600D gas chromatograph with a tritium foil electron-capture detector, glass column 6 ft × 0.125 in. (o.d.), 3% OV-17, Chromosorb W, AW-DMCS, HD (100–120 mesh), N_2 30 ml/min, oven 200° was used. The amide (300 pg) was detected.

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