

Asymmetric Synthesis of Psychotomimetic Phenylisopropylamines¹

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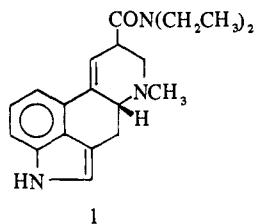
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The enantiomers of a series of methoxy- and alkyl-substituted phenylisopropylamines were prepared by low-pressure reduction of imines formed by reaction of the appropriate phenylacetones with either (+)- or (-)- α -methylbenzylamine, followed by hydrogenolysis of the hydrochlorides of the resulting *N*-(α -phenethyl)phenylisopropylamines. Values of $[\alpha]_D$ are reported and enantiomeric purities were in the range 96–99%. Overall yields ranged from 30 to 60%. Glc or fluorine nmr analysis of enantiomeric purity was accomplished using α -methoxy- α -trifluoromethylphenylacetamides. Glc analysis of the *N*-trifluoroacetyl-*S*-prolylamides was used to confirm *R*-(-) and *S*-(+) absolute configurations of all compounds. (+)- or (-)-2,5-dimethoxyamphetamine was brominated to give the (+)- or (-)-4-bromo compound. The enantiomers of 1,2,3,4-tetrahydro-2-naphthylamine could not be prepared by this method.

Generally, optical isomers of a drug molecule possess differing degrees of biological activity. In the case of amphetamine, norepinephrine uptake into synaptosomes from noradrenergic regions of the brain is inhibited to a greater degree by the *S*-(+) than by the *R*-(-) enantiomer.^{2,3} In addition, the two isomers of amphetamine are not equally good substrates for side-chain metabolizing enzymes in certain animal species.⁴ Since Gordis⁵ has found that no racemization of either isomer occurs when amphetamine is administered to man, it is possible that the complex effects of psychotomimetic amphetamines could be partially due to the fact that racemic mixtures have been used for testing.

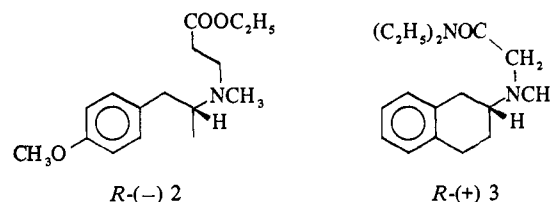
In the report by Barfknecht and Nichols⁶ on the effects of (*R*)-(-) and (*S*)-(+)-3,4-dimethoxyamphetamine (3,4-DMA) in the rat, it was suggested that LSD could be considered as a phenethylamine derivative. Natural lysergic acid **1** possesses



the *5R,8R* absolute configuration^{7,8} and it was predicted that the psychotomimetic effects of the amphetamines might reside in the *R* enantiomers, based on their stereochemical relationship to lysergic acid. This prediction is consistent with stereochemical correlations between LSD, phenethylamines, and tryptamines proposed by Kang and Green.⁹ Indeed, it was found that the *R*-(-) isomer of 3,4-DMA seemed to be responsible for the psychotomimetic effects in the rat.⁶ Shulgin¹⁰ has recently determined that the *R*-(-) enantiomer is responsible for the sensory and hallucinatory effects of 2,5-dimethoxy-4-methylamphetamine (DOM, STP). Benington, et al.,[†] have observed that the *R*-(-) isomer is also responsible for the psychotomimetic effects of 2,5-dimethoxy-4-bromoamphetamine (DOB)^{11,12} in the rat.

Although LSD has only recently been considered as a phenethylamine,^{6,9,13} this approach was used in earlier literature in relation to the oxytocic activity of other lysergic acid alkaloids.¹⁴⁻¹⁶ Plieninger¹⁶ resolved *N*-methyl-*p*-methoxyam-

phetamine and studied the oxytocic activity of the ethyl acrylate adducts. He found the levo isomer **2** to be more potent than the dextro. Marini-Bettolo and coworkers¹⁷ resolved the 2-aminotetralin derivative **3** and found that the dextro isomer possessed the lysergic acid-like activity. Although the signs of rotation were reported for **2** and **3**,



the absolute configurations were unknown at that time. More recent studies have shown that a number of *N*- and ring-substituted amphetamines all possess the *R*-(-) absolute configuration.¹⁸⁻²¹ Unsubstituted 2-aminotetralin has been shown to have the *R*(+) configuration.²² Considering Tchugaeff's rule²³ and based on Beckett and Brooks work,²⁰ one would not expect *N* substitution to affect the sign of rotation and **3** would also be predicted to have the *R*(+) configuration. Indeed, this assumption would seem to be confirmed by the fact that LSD itself possesses the *R*(+) absolute configuration. Thus, both **2** and **3** have the *R* configuration and correlate with lysergic acid. Cooper and Walters have recently tested *cis*- and *trans*-2-(3,4,5-trimethoxyphenyl)cyclopropylamine as analogs of mescaline.²⁴ Their data indicate that the phenethylamine-type psychotomimetics interact with the receptor in a *transoid* conformation which finding is also consistent with the above correlations. Although these examples have arisen from a search for better oxytocic agents, one may speculate that they reflect the action of the lysergic acid nucleus itself.

It was deemed desirable to develop a practical method for preparing the pure *R* and *S* enantiomers of variously substituted amphetamines for pharmacological study. Unfortunately, classical resolution techniques are tedious, usually afford poor yields, and may not be generally applicable.

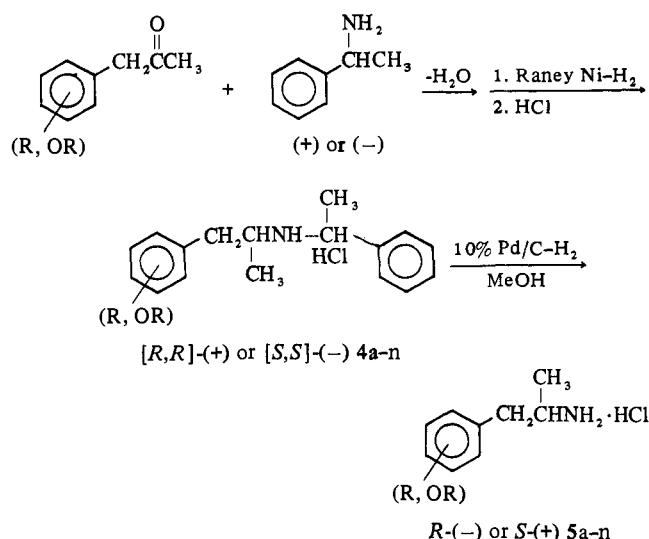
Discussion and Results

We now report the asymmetric synthesis of alkyl- and methoxyl-substituted amphetamines based on a modification of the method of Weinges and Graab.²⁵ This method gives superior yields and utilizes more convenient procedures than

[†]F. Benington, R. D. Morin, J. R. Smythies, J. M. Beaton, and R. J. Bradley, unpublished results.

the original method. In Weinges and Graab's procedure 3,4-dimethoxyphenylacetone was mixed with (+)- or (-)- α -methylbenzylamine and shaken at 100 atm of H₂ over Raney Ni. The hydrochlorides of the resulting *N*-(α -phenethyl)-phenylisopropylamines were then hydrogenolyzed over reduced PdCl₂. Yields in the initial reduction were low, and the subsequent hydrogenolysis step required about 5 days for completion. In our modification, the imines were preformed from the phenylacetone and the α -methylbenzylamine by azeotropic water removal in refluxing benzene. The resulting imines were not isolated but were reduced directly at 50 psig in a Parr shaker. Moderate yields were obtained. The hydrogenolysis step proceeded usually in quantitative yield in less than 36 hr using 10% Pd/C catalyst. The procedure is general and has been extended to a large number of ring-methoxylated amphetamines. The route is represented by Scheme I.

Scheme I



The appropriately substituted phenylacetones were either obtained commercially or were prepared by Fe-HCl reduction of the corresponding 1-phenyl-2-nitropropenes.²⁶ All had been reported in the literature with the exception of the 2,5-dimethoxy-4-ethylphenylacetone, whose synthesis is described in the Experimental Section. The nitropropenes were prepared by condensation of the substituted benzaldehydes with EtNO₂.²⁷ All aldehydes and nitropropenes have

been reported previously with the exception of the 2,5-dimethoxy-4-ethyl compounds, whose syntheses are also described.

Tabulated results for the preparation of compounds 4a-n are given in Table I. The summary of data from the preparation of compounds 5a-p is presented in Table II. Highest enantiomer purity (compounds 5c and 5m) was obtained by several recrystallizations of the *N*-(α -phenethyl) precursors 4c and 4m. This indicates that final purity is dependent on the purity of the diastereomeric intermediates. However, a single recrystallization sufficed to give enantiomeric purities of final compounds in the range 96-97%.

TPC amides were used to confirm absolute configuration. As pointed out by Westley, *et al.*,²⁸ regarding *N*-trifluoroacetyl-*S*-prolylamides, the *S,S* diastereomer always elutes after the *S,R* form. Although stereospecificity of the asymmetric synthesis is strong, presumptive evidence for predicting the absolute configuration of the enantiomers, the order of elution of the TPC amides confirmed that in every case the compounds which were prepared possessed the *R*(-) and *S*(+) configurations.

In the glc analysis of enantiomer purity using the α -methoxy- α -trifluoromethylphenylacetamides (MTPA amides), retention times were in the order of 20-30 min with a typical separation of 4-6 min between diastereomers. It was found that the (-)-amine-(+)-MTPA or (+)-amine-(-)-MTPA amides had longer retention times than the (-)-amine-(-)-MTPA or (+)-amine-(+)-MTPA amides. Dale, *et al.*,²⁹ have presented evidence which suggests that MTPA has the *R*(+) absolute configuration. If this assignment is correct, the order of elution of the diastereomers is *R,S* or *S,R* before *R,R* or *S,S*. This result would be consistent with the findings of Westley, *et al.*,²⁸ as discussed above.

Use of *N*-trifluoroacetyl-*S*-prolylamides (TPC amides) for enantiomer purity analysis was complicated by racemization of the reagent. Although TPC reagent is inexpensive and has been used successfully^{5,28,30} for analysis for enantiomeric purity of amphetamine, we obtained variable results apparently caused by racemization during preparation of the amides. Using a standard sample of (-)- α -methylbenzylamine of known (99+%) enantiomeric purity, it was found that the apparent purity varied from 85 to 95%. This seemed to be related to the length of time the amide preparations were allowed to stand before work-up. Racemization occurred either during reagent preparation or during formation of the amides. It is possible that in the presence of amines race-

Table I. Substituted *N*-(α -Phenethyl)phenylisopropylamine Hydrochlorides (4a-n)

Compd	Ar substitution	Isomer	[α] ^{25D} , deg (c 2, MeOH)	Mp, °C (cor)	Yield, %	Formula	Analyses
4a	Unsubstituted	<i>R,R</i> (+)	+21.0	233.5-234.5	70.5	C ₁₇ H ₂₂ ClN	C, H, N
4b	3,4-(OMe) ₂	<i>S,S</i> (-)	-20.5	216-217	48	C ₁₉ H ₂₆ ClNO ₂	C, H, N
4c	4-OMe	<i>R,R</i> (+)	+36.1	195-197	40	C ₁₈ H ₂₄ ClNO	C, H, N
4d	4-OMe	<i>S,S</i> (-)	-36.1	195-197	57.5	C ₁₈ H ₂₄ ClNO	C, H, N
4e	2,3-(OMe) ₂	<i>R,R</i> (+)	+22.1	181-182	32	C ₁₉ H ₂₆ ClNO ₂	C, H, N
4f	2,3-(OMe) ₂	<i>S,S</i> (-)	-21.7	180-181		C ₁₉ H ₂₆ ClNO ₂	C, H, N
4g	2,5-(OMe) ₂	<i>R,R</i> (+)	+7.50	227-228	63	C ₁₉ H ₂₆ ClNO ₂	C, H, N
4h	2,5-(OMe) ₂	<i>S,S</i> (-)	-7.75	227-228	67	C ₁₉ H ₂₆ ClNO ₂	C, H, N
4i	3,4,5-(OMe) ₃	<i>R,R</i> (+)	+4.00	223-224.5	67	C ₂₀ H ₂₈ ClNO ₃	C, H, Cl
4j	3,4,5-(OMe) ₃	<i>S,S</i> (-)	-4.24	223.5-224.5	68	C ₂₀ H ₂₈ ClNO ₃	C, H, Cl
4k	2,5-(OMe) ₂ -4-Me	<i>R,R</i> (+)	+7.38	198-199	44	C ₂₀ H ₂₈ ClNO ₂	C, H, Cl
4l	2,5-(OMe) ₂ -4-Me	<i>S,S</i> (-)	-7.18	195-196.5	41	C ₂₀ H ₂₈ ClNO ₂	C, H, Cl
4m	2,5-(OMe) ₂ -4-Et	<i>R,R</i> (+)	+11.2	214-214.5	40	C ₂₁ H ₃₀ ClNO ₂	C, H, N
4n	2,5-(OMe) ₂ -4-Et	<i>S,S</i> (-)	-11.4	213.5-214.5	24	C ₂₁ H ₃₀ ClNO ₂	C, H, N

Table II. Substituted Phenylisopropylamine Hydrochlorides (5a-p)

Compd	Ar substitution	Isomer	[α] ²⁵ D, deg (c 2, H ₂ O)	ArCH ₂ CHNH ₂ ·HCl		% yield ^a	Enantiomer purity, %	Formula	Analyses
				[M]D	Mp, °C (cor)				
5a	Unsubstituted	R(-)	-27.2 ^b	46.7	157-158	83	100 ^e	C ₉ H ₁₄ ClN	C, H, N
5b	3,4-(OMe) ₂ (3,4-DMA)	S(+)	+23.1 ^c	53.5	141-142	90	97 ^d	C ₁₁ H ₁₈ ClNO ₂	C, H, N
5c	4-OCH ₃ (PMA)	R(-)	-22.5	45.4	251-253	62	99, ^d 100 ^e	C ₁₀ H ₁₆ ClNO	C, H, N
5d	4-OCH ₃	S(+)	+22.4	45.2	250.5-251.5	68		C ₁₀ H ₁₆ ClNO	C, H, N
5e	2,3-(OMe) ₂ (2,3-DMA)	R(-)	-16.9	39.2	124-125	92	97 ^d	C ₁₁ H ₁₈ ClNO ₂	C, H, N
5f	2,3-(OMe) ₂	S(+)	+16.6	38.5	123-124	90		C ₁₁ H ₁₈ ClNO ₂	C, H, N
5g	2,5-(OMe) ₂ (2,5-DMA)	R(-)	-18.7	43.3	145-146	87	96, ^d 100 ^e	C ₁₁ H ₁₈ ClNO ₂	C, H, N
5h	2,5-(OMe) ₂	S(+)	+18.0	41.7	144-145	90	96 ^d	C ₁₁ H ₁₈ ClNO ₂	C, H, N
5i	3,4,5-(OMe) ₃ (TMA)	R(-)	-17.7	46.3	206-208	84		C ₁₂ H ₂₀ ClNO ₃	C, H, N
5j	3,4,5-(OMe) ₃	S(+)	+17.3	45.3	206-208	82		C ₁₂ H ₂₀ ClNO ₃	C, H, N
5k	2,5-(OMe) ₂ -4-Me (DOM)	R(-)	-17.2	42.3	204-205	83	96 ^d	C ₁₂ H ₂₀ ClNO ₂	C, H, N
5l	2,5-(OMe) ₂ -4-Me	S(+)	+17.2	42.3	204-205	82		C ₁₂ H ₂₀ ClNO ₂	C, H, N
5m	2,5-(OMe) ₂ -4-Et (DOEt)	R(-)	-16.1	41.8	226.5-227	97	99 ^d	C ₁₃ H ₂₂ ClNO ₂	C, H, N
5n	2,5-(OMe) ₂ -4-Et	S(+)	+16.0	41.6	225.5-226.5	97	97 ^d	C ₁₃ H ₂₂ ClNO ₂	C, H, N
5o	2,5-(OMe) ₂ -4-Br (DOB)	R(-)	-13.7	42.5	203.5-204	54.5 ^f		C ₁₁ H ₁₇ BrClNO ₂	C, H, N
5p	2,5-(OMe) ₂ -4-Br	S(+)	+13.7	42.5	204-205	54.5 ^f	100 ^e	C ₁₁ H ₁₇ BrClNO ₂	C, H, N

^aQuantitative yields of slightly depressed melting points are obtained; reported yields are recrystallized. ^b[α]_D 24.8°: W. Leithe, *Chem. Ber.*, 65, 664 (1932). ^cLit.²¹ [α]_D 23°. ^dDetermined by glc analysis of MTPA amides. ^eDetermined by fluorine nmr of MTPA amides. ^fYields based on 2,5-DMA starting material.

Table III. Nmr Chemical Shifts of Diastereomeric Amides of (+)- or (-)- α -Methoxy- α -trifluoromethylphenylacetamides

Diastereomer	Amine configuration	Chemical shifts of diastereomers in Hz downfield of trifluoroacetic acid
(-)-Amphetamine	R	687
(+)-MTPA		
(-)- <i>p</i> -Methoxyamphetamine	R	686
(+)-MTPA		
(-)-2,5-Dimethoxyamphetamine	R	675
(-)-MTPA		
(+)-2,5-Dimethoxy-4-bromoamphetamine (+)-MTPA	S	660

mization proceeds through a ketene intermediate. It is more reliable to use the MTPA amides in which no possibility for racemization exists.

Enantiomeric purity of several isomers was also determined by fluorine nmr of the MTPA amides as described by Dale, *et al.*,²⁹ and these data are tabulated in Table III. Purity appeared to be 100% for compounds analyzed by this method, whereas glc analysis indicated that this value was too high. As expected, the glc technique for analysis of purity is more sensitive.

Molar rotations were calculated for the amphetamines and are listed in Table II. It will be noted that the values for 2,5-DMA (5g,h), DOM (5k,l), DOEt (5m,n), and DOB (5o,p) are very similar ($\bar{x} = 42.25 \pm 0.52$). The data indicate that for 2,5-dimethoxy-substituted series, [α]_D depends only on the atomic weight of the para substituent. It seems likely that this value of [M]D could be used to predict values of [α]_D for other members of the series such as the *p*-methoxy (TMA-2) or the *p*-chloro derivatives. No similar correlation seems to exist between other compounds in Table II. An attempt to extend this method of synthesis to preparation

of the enantiomers of 2-aminotetralin resulted in optical purity of only 5-10%.²²

Experimental Section

Melting points were determined in open glass capillaries using a Thomas-Hoover Uni-Melt apparatus and are corrected. Elemental analyses were performed by Midwest Microlab, Ltd., Indianapolis, Ind., or by the Microanalytical Laboratory of the Division of Medicinal Chemistry, University of Iowa. Where analyses are indicated by symbols of the elements, the analytical results obtained were within $\pm 0.4\%$ of the calculated values. Optical rotations were measured with a Perkin-Elmer Model 141 polarimeter using 2% solutions in MeOH or H₂O as indicated. Glc analyses were performed on a Hewlett-Packard Model 5750 gas chromatograph equipped with a flame ionization detector. Fluorine nmr were run on a Varian Associates HA-100 spectrometer (94.1 MHz) and chemical shifts were measured in 80% CDCl₃ relative to an internal standard of 20% CF₃COOH.

2,5-Dimethoxy-4-ethylbenzaldehyde. This was prepared by a modification of the method of Rieche, *et al.*³¹ 2,5-Dimethoxyethylbenzene³² (66.4 g, 0.4 mol) was dissolved in 250 ml of dry CH₂Cl₂ and cooled to 10° and 208 g (0.8 mol) of anhydrous SnCl₄ was added. Cl₂CHOCH₃ (45.9 g, 0.4 mol) was then added over 40 min, maintaining the temperature at 5-10°. The solution was allowed to warm to room temperature over 45 min, heated under reflux for 1 hr, cooled, and poured over 500 g of ice-H₂O. The aqueous layer was discarded. The CH₂Cl₂ layer was washed with 3 N HCl and H₂O and dried (Na₂SO₄). After removal of the solvent the residue was triturated with saturated NaHSO₃ solution. The addition product was dissolved in H₂O; the aqueous solution was washed with Et₂O and then decomposed with Na₂CO₃ solution. On cooling, the aldehyde solidified, was collected by filtration, and recrystallized from MeOH-H₂O: yield 42 g (54%); mp 46-47°. *Anal.* (C₁₁H₁₄O₃) C, H.

1-(2,5-Dimethoxy-4-ethylphenyl)-2-nitropropene was prepared by condensation of the above aldehyde with EtNO₂ in AcOH containing NH₄OAc.²⁷ The yellow product was recrystallized from MeOH: yield 60.8%; mp 63-64°. *Anal.* (C₁₃H₁₇NO₄) C, H, N.

1-(2,5-Dimethoxy-4-ethylphenyl)-2-propanone. This substituted phenylacetone was prepared by Fe-HCl reduction of the above nitro compound by the method of Haas:²⁶ yield 60%; bp 131-132° (0.1 mm); characterized as the oxime, mp 79.5-80.5°. *Anal.* (C₁₃H₁₉NO₃) C, H, N.

(*R,R*)-(+)- or (*S,S*)-(-)-Substituted *N*-(α -Phenethyl)phenylisopropylamine Hydrochlorides (4a-n). The appropriate phenylacetone, 0.05 mol, and 0.05 *M* of either (*R*)-(+)- or (*S*)-(-)- α -methylbenzylamine (Aldrich) were heated together under reflux in 50 ml of C₆H₆ for 24 hr with continuous H₂O removal.[‡] The C₆H₆ was removed, the residue dissolved in 50 ml of absolute EtOH, and the resulting solution shaken over 2 g of EtOH-washed W-2 Raney Ni at 50 psig of H₂ until the calculated amount of H₂ was absorbed, usually within 24 hr. The mixture was filtered through sintered glass;[§] the filtrate was acidified with EtOH-HCl and concentrated to small volume. The HCl salt precipitated upon dilution with Et₂O and was recrystallized from Me₂CO-H₂O or Me₂CO-*i*-PrOH.

(*R*)-(-)- or (*S*)-(+)-Substituted Phenylisopropylamine Hydrochlorides (5a-n). To a slurry of 0.35 g of 10% Pd/C in several milliliters of H₂O was added 90 ml of MeOH and 5 g of either the (*R,R*)-(+)- or (*S,S*)-(-)-*N*-(α -phenethyl)phenylisopropylamine HCl prepared above. The mixture was shaken at 50 psig of H₂. The calculated uptake usually occurred within 48 hr (reduced amounts of catalyst greatly prolonged this time). The mixture was filtered and concentrated to dryness, and the residue was recrystallized from *i*-PrOH-Et₂O.

(+)- or (-)-2,5-Dimethoxy-4-bromoamphetamine Hydrochloride (5o,p). Bromination was accomplished by the method of Harley-Mason.³³ The free base (1.62 g, 8.3 mmol) of either (+)- or (-)-2,5-DMA was dissolved in 6 ml of AcOH. A solution of 1.33 g (8.3 mmol) of Br₂ in 4.5 ml of AcOH was added over 10 min and the solution stirred 24 hr at room temperature. The mixture was diluted to 200 ml with Et₂O and the HBr salt precipitated. The salt was collected by filtration, neutralized with 10% NaOH, taken up into Et₂O, and precipitated as the HCl salt with dry HCl. The salt was recrystallized from *i*-PrOH, yield 1.40 g (54.5%).

Preparation of MTPA Amides.²⁹ (+)- or (-)-Methoxytrifluoromethylphenylacetic acid (MTPA, Aldrich) (1 g) was refluxed 12 hr with 10 ml of SOCl₂. The SOCl₂ was removed and the MTPA-Cl diluted with 1 ml of dry pyridine and 4.6 ml of CHCl₃. The amphetamine HCl (0.5 mmol) was dissolved in 0.25 ml of pyridine and 0.5 ml of CHCl₃ and allowed to sit overnight with one-fourth of the MTPA-Cl solution (ca. 1.05 mmol). The solution was diluted to 10 ml with CHCl₃ and washed with 3 *N* HCl, 5% NaHCO₃, and H₂O. The CHCl₃ solution was dried (Na₂SO₄), the CHCl₃ removed, and the residue recrystallized from C₆H₆-hexane. This was difficult in most cases and analyses were usually carried out on the crude viscous amide.

Glc Analysis of MTPA Amides. A copper column, 1.33 m \times 3.18 mm i.d., packed with 2% Carbowax 20M on 80-100 mesh Gas Chrom Q (Applied Science Labs) was used. The column was conditioned for 24 hr at 225° before use and operated at the same temperature. The He carrier gas flow was adjusted to ca. 100 ml/min. Sample and detector temperatures were set at 300°. A 5- μ l volume containing 5-10 μ g of the MTPA amide was injected and the per cent composition determined by cutting out the peaks and integrating the area by direct weighing.

Preparation of *N*-Trifluoroacetyl-S-prolylamides and Determination of Absolute Configuration. *N*-Trifluoroacetyl-S-prolyl chloride (TPC) reagent was prepared by the method of Weygand, *et al.*,³⁴ or by the method of Wells.³⁰ (TPC reagent is available from Regis Chemical Co.) Amides of the amphetamine isomers were prepared

[‡] Addition of a few drops of AcOH did not decrease the reaction time.

[§] The catalyst is extremely pyrophoric.

and analyzed using the same column and conditions as was described for the MTPA amides.

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