

Synthesis of *S*(+) and *R*(-)-3-(2-Aminopropyl)indole from Ethyl-D- and L-Tryptophanate

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Received March 8, 1976

A stereospecific requirement for hallucinogenesis applies to certain molecules containing an asymmetric center. Thus, only the *R*-isomers of substituted phenylisopropylamines and lysergic acid diethylamide are psychotomimetic. The enantiomers of a minor hallucinogen, *S*(+)- and *R*(-)-3-(2-aminopropyl)indole (α -methyltryptamine) (**6a** and **6b**) were synthesized *via* a 5-step manipulation from D- and L-tryptophan ethyl ester hydrochloride, respectively. Optical purity of these two isomers was determined by pmr spectroscopy of their complexes with a europium chiral shift reagent using the indole C₂H signal.

J. Heterocyclic Chem., **13**, 775 (1976).

Although it has been known for many years that only the 5*R*;8*R* isomer of lysergic acid diethylamide (**1**) possesses hallucinogenic activity, it has only recently been shown that this asymmetric requirement applies to other psychotomimetic molecules. Thus, a number of reports (2-6) have appeared which attribute the hallucinogenic properties of substituted phenylisopropylamines to the *R*(-)-enantiomers. An asymmetric synthesis of these compounds has been developed (7).

The psychotomimetic effects of *dl*- α -methyltryptamine in man were reported by several investigators in the early 1960's (8,9). Originally evaluated as a monoamine oxidase inhibitor (10) its central effects precluded clinical use.

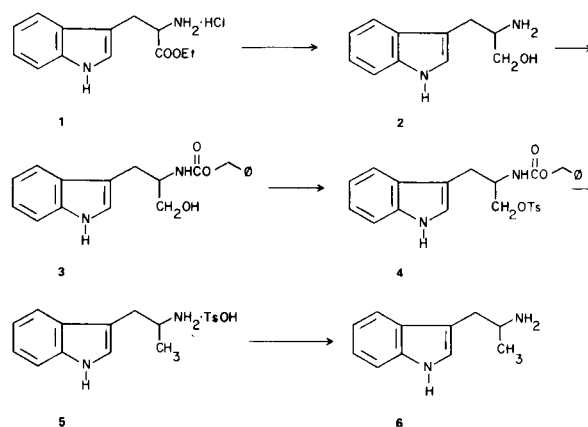
In their review of the pharmacology of hallucinogens, Brawley and Duffield (11) have stated ". . . no single behavioural parameter in animals correlates reliably with hallucinogenic effect in man." However, there appears to be a significant correlation between central stimulant-induced stereotyped behavior in various animal species and humans (12).

Dewhurst and Marley (13) demonstrated the central stimulant effects of (+)- α -methyltryptamine in chickens and found it to be four times as active as (+)-amphetamine in terms of threshold dose and that the (+)-isomers were four times as active as the (-)-isomers. Similar stereotyped hyperactivity in rats produced by *d*-amphetamine and *dl*- α -methyltryptamine was described by Randrup, Munkvad

and Udsen (14). Other investigators (15) noted the amphetamine-like effects of *dl*- α -methyltryptamine on mouse locomotion with an ED₅₀ six times higher than that of amphetamine. In view of these results we wish to report the synthesis of (+)- and (-)- α -methyltryptamine from readily available starting materials.

A number of synthetic routes to α -alkyltryptamines have been elaborated (16-19), all of them leading to the preparation of a racemic mixture. Potapov, Terent'ev, Preobrazhenskaya and Suvorov (20) resolved *dl*- α -methyl-

Scheme I



tryptamine *via* the tartrate salts. These investigators found that the (-)-isomer had the same configuration as (-)-amphetamine based on the similarity of the ORD curves.

Since the absolute configuration of L-tryptophan has been determined as *S* by both chemical (21) and biological (22) means, the Sequence Rule of Cahn, Ingold and Prelog

Table I

Compound	Isomer	$[\alpha]_D^{25}$, deg (c, methanol)	M.p. °C (corr)	Formula	Analyses
2a	R(+)	+20.9 (1.0) (a)	80-81	C ₁₁ H ₁₄ N ₂ O (190.25)	Calcd.: C, 69.45; H, 7.42; N, 14.73. Found: C, 69.24; H, 7.31; N, 14.67.
2b	S(-)	-20.5 (1.0) (a)	84-85	"	Found: C, 69.29; H, 7.23; N, 14.48.
3a	R(+)	+39.0 (1.0)	108-109	C ₁₉ H ₂₀ N ₂ O ₃ (324.39)	Calcd.: C, 70.35; H, 6.21; N, 8.64. Found: C, 70.24; H, 6.16; N, 8.57.
3b	S(-)	-39.0 (0.9)	107-108	"	Found: C, 70.50; H, 6.25; N, 8.59.
4a	R(+)	+21.0 (2.6)	(b)	C ₂₆ H ₂₆ N ₂ O ₅ S (478.60)	Calcd.: C, 65.25; H, 5.48; N, 5.85. Found: C, 65.53; H, 5.57; N, 5.59.
4b	S(-)	-22.8 (1.1)	(b)	"	Found: C, 65.39; H, 5.71; N, 5.71.
5a	S(+)	+ 8.4 (0.9)	152-153	C ₁₈ H ₂₂ N ₂ O ₃ S (346.50)	Calcd.: C, 62.40; H, 6.40; N, 8.09. Found: C, 62.63; H, 6.39; N, 8.07.
5b	R(-)	- 9.5 (0.7)	151-152	"	Found: C, 62.62; H, 6.44; N, 7.95.
6a	S(+)	+34.9 (0.9) (c)	125-126	C ₁₁ H ₁₄ N ₂ (174.25)	Calcd.: C, 75.82; H, 8.10; N, 16.08. Found: C, 75.61; H, 8.18; N, 15.97.
6b	R(-)	-32.1 (1.0) (c)	126-127	"	Found: C, 75.65; H, 8.00; N, 15.86.

(a) Jones, Sneddon and Lewis, *Biochim. Biophys. Acta*, **341**, 284 (1974) report $[\alpha]_D +22.8^\circ$ and -20.6° , for **2a** and **2b**, respectively. (b) This compound was characterized as a homogeneous foam. (c) Reference 15 reports $[\alpha]_D +34.7^\circ$ and -34.8° for **6a** and **6b**, respectively.

Table II

Proton Magnetic Resonance Parameters (a)

Compound	Solvent	Chemical shift, ppm (δ) downfield from tetramethylsilane
2a	DMSO d-6	7.48 (dd, 1H, $J_{4,5} = 7.0$ Hz, $J_{4,6} = 2.0$ Hz, C ₄ H), 7.42 (dd, 1H, $J_{6,7} = 7.0$ Hz, $J_{5,7} = 2.0$ Hz, C ₇ H), 7.14 (d, 1H, $J_{1,2} = 2.0$ Hz, collapsing to s on addition of deuterium oxide, C ₂ H), 7.03 (m, 2H, C ₅ H and C ₆ H), 3.36 (m, 2H, CH ₂ OH), 3.01 (m, 2H, β -CH ₂), 2.75 (dd, 1H, α -CH).
3a	Deuteriochloroform	8.14 (br s, 1H, N ₁ H, exc. deuterium oxide), 7.61 (br m, 1H, C ₄ H), 7.30 (s, 5H, ϕ -H), 7.15 (m, 3H, C ₅ H, C ₆ H and C ₇ H), 6.93 (d, 1H, $J_{1,2} = 2.5$ Hz, sharpening to s on addition of deuterium oxide, C ₂ H), 5.08 (s, 2H, ϕ -CH ₂), 4.01 (br m, 1H, α -CH), 3.60 (m, 2H, CH ₂ OH), 2.98 (d, 2H, $J_{\alpha,\beta} = 7.0$ Hz, β -CH ₂), 2.57 (br s, 1H, OH, exc. deuterium oxide).
4a	Deuteriochloroform	8.10 (br s, 1H, N ₁ H, exc. deuterium oxide), 7.74 (d, 2H, $J = 8.0$ Hz, tosyl Ar-H), 7.57 (m, 1H, C ₄ H), 7.32 (s, 5H, ϕ -H), 7.29 (d, 2H, $J = 8.0$ Hz, tosyl Ar-H), 7.16 (m, 3H, C ₅ H, C ₆ H and C ₇ H), 6.94 (s, 1H, sharpening on addition of deuterium oxide, C ₂ H), 5.06 (s, 2H, ϕ -CH ₂), 4.18 (br m, 1H, α -CH), 3.00 (br d, 2H, $J_{\alpha,\beta} = 6.0$ Hz, β -CH ₂), 2.41 (s, 3H, ϕ -CH ₃).
6a	Deuteriochloroform	8.60 (br s, 1H, N ₁ H, exc. deuterium oxide), 7.65 (m, 1H, C ₄ H), 7.26 (m, 3H, C ₅ H, C ₆ H and C ₇ H), 6.99 (s, 1H, sharpening on addition of deuterium oxide, C ₂ H), 3.52 (br m, 1H, α -CH), 2.80 (complex m, 2H, β -CH ₂), 1.32 (br s, 2H, NH ₂), 1.18 (d, 3H, CH ₃).

(a) Pmr data for the other isomers is identical

(23) would establish the configuration of the end product (**6b**) of Scheme 1 as *R* in the case of *S*-tryptophan. The actual stereochemistry of **2-6** is preserved since the asymmetric center is not affected by the reaction conditions. The enantiomeric purity of **6a** and **6b** was established by proton magnetic resonance using Eu-Optishift II [tris-(3-(heptafluoropropylhydroxymethylene)-*d*-camphorato) europium (III) (**24**), supplied by Willow Brook Laboratories, Inc., Waukesha, Wisconsin]. The most satisfactory signal in the pmr spectrum of **6** for this analysis is C₂H of the indole ring at 6.99 ppm (δ). This signal approximates a singlet which is clearly resolved in the presence of the Optishift reagent. The pmr spectrum of the europium complexes of a prepared mixture of 70% **6a**/30% **6b** showed distinctly resolved signals for the indole-2-proton in the ratio of 7:3. At a molar ratio of shift reagent to **6** of 1:1 the chemical shift of C₂H in **6a** is 11.10 ppm and **6b** is 11.00 ppm. Based on the spectra of the enantiomers of **6** the optical purity of each appears to be at least 97%. This evidence combined with the optical rotational measurements of **6a** and **6b** makes us confident that the reaction sequence outlined in Scheme 1 proceeds without racemization.

Preliminary pharmacological testing showed a distinct quantitative difference in biological activity for **6a** and **6b**. Following administration, mice were observed for stereotyped hyperactivity according to the procedure of Randrup and Munkvad (12,14). The minimum effective dose found to induce this effect was 16 mg./kg. for **6a** and 64 mg./kg. for **6b**. Toxicity paralleled these results with LD₅₀ of 24 mg./kg. for **6a** and 100 mg./kg. for **6b**. Other investigators reported an LD₅₀ of 38 mg./kg. for racemic α -methyl-tryptamine in mice (25).

EXPERIMENTAL

Tlc was carried out using silica gel GF on glass plates obtained from Analtech Inc., Newark, Delaware. Preparative tlc was done using 1.0 mm layers of silica gel GF on 20 x 20 cm glass plates. Elemental analyses were performed by Galbraith Laboratories, Inc., Knoxville, Tennessee. Optical rotations were measured with a Perkin-Elmer Model 141 polarimeter. Proton magnetic resonance spectra were run on a Varian Associates XL-100 spectrometer with an internal standard of tetramethylsilane. Europium shift studies were carried out in deuteriochloroform. Physical constants for **2-6** are noted in Table I. *D*- and *L*-tryptophan ethyl ester hydrochlorides were obtained from Nutritional Biochemicals Inc., Cleveland, Ohio. The synthetic procedure is illustrated for **2a** to **6a** only. Male albino mice (ICR Strain) weighing 23-27 g. were given **6a** and **6b** subcutaneously as the hydrochlorides in 0.9% saline.

R(+)-2-Amino-3-(3-indolyl)propanol (**2a**).

One g. (3.58 mmoles) of *D*-tryptophan ethyl ester hydrochloride was added in portions to a stirred suspension of 800 mg. (21 mmoles) of lithium aluminum hydride in 15 ml. of dry tetrahydrofuran at room temperature. After stirring for 30 minutes,

the complex was decomposed by dropwise addition of 2*N* sodium hydroxide. The solids were filtered and shaken with 50 ml. of 2*N* sodium hydroxide and 200 ml. of chloroform in a separatory funnel. The organic layer was separated, combined with the original filtrate and dried (magnesium sulfate). The drying agent was removed by filtration and the filtrate concentrated at reduced pressure. The syrupy residue was crystallized from ethyl acetate/hexane, 450 mg. (66%).

R(+)-*N*-(Benzyloxycarbonyl)-2-amino-3-(3-indolyl)propanol (**3a**).

Compound **2a** (1.32 g., 6.95 mmoles) was dissolved in a mixture of 30 ml. of water and 30 ml. of acetone. Sodium carbonate (1.27 g., 12 mmoles) was added and to the stirred, cooled mixture (ice) was added dropwise 1.0 ml. (7.0 mmoles) of benzyl chloroformate. After the addition the cooling bath was removed and the reaction stirred at room temperature for 1.5 hours. The reaction mixture was acidified (to pH 2) with concentrated hydrochloric acid and diluted with 100 ml. of water. The aqueous mixture was extracted with 2 x 150 ml. of ethyl acetate, the organic solution washed with 100 ml. of saturated aqueous sodium chloride and dried (magnesium sulfate). Filtration of the drying agent and concentration *in vacuo* left a syrupy residue which was crystallized from chloroform/hexane to give 1.7 g. (75%).

R(+)-*N*-(Benzyloxycarbonyl)-2-amino-3-(3-indolyl)propanol *p*-Toluenesulfonate (**4a**).

Compound **3a** (350 mg., 1.08 mmoles) was dissolved in 10 ml. of dry pyridine and 310 mg. (1.62 mmoles) of *p*-toluenesulfonyl chloride was added. The reaction was stored at room temperature for 18 hours and the solvent distilled under reduced pressure. The residue was partitioned between 200 ml. of ethyl acetate and 50 ml. of saturated aqueous sodium chloride. The organic layer was washed with 50 ml. of water and dried (magnesium sulfate). Filtration and concentration *in vacuo* left a foamy residue. Pure **4a** was isolated by preparative tlc using 10% acetone in benzene, 400 mg. (77%). This compound was unstable at room temperature but could be stored for several weeks at -15°C.

S(+)-3-(2-Aminopropyl)indole *p*-Toluenesulfonate (**5a**).

Compound **4a** (400 mg., 0.84 mmole) was dissolved in 25 ml. of absolute ethanol and 100 mg. of 10% palladium on charcoal catalyst added. The reaction mixture was shaken under 3 atmospheres of hydrogen for one hour. The catalyst was filtered (Celite) and the filtrate concentrated under reduced pressure. The residual oil was taken up in 6 ml. of hot chloroform and cooled to room temperature. The precipitate was filtered and dried *in vacuo*. It was recrystallized from methanol/ether, 240 mg. (82%).

S(+)-3-(2-Aminopropyl)indole (**6a**).

Compound **5a** (100 mg., 0.289 mmole) was stirred in 10 ml. of 2*N* sodium hydroxide for 5 minutes. The oily product was extracted with 2 x 50 ml. of ethyl acetate and the organic solution was dried (magnesium sulfate), filtered and concentrated under reduced pressure. The syrupy residue was crystallized from ethyl acetate/hexane, 35 mg. (69%).

Acknowledgments.

We wish to thank Dr. Lois Durham and Dr. Glenn Sullivan of the NMR Laboratory, Department of Chemistry, Stanford University, for obtaining the pmr spectra, europium shift studies and their helpful discussion concerning these spectra. We also wish to express our gratitude to Dale T. Leslie for his capable assistance with animal studies.

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