SYNTHESIS OF PSILOCIN LABELLED WITH ^{14}C AND ^{3}H

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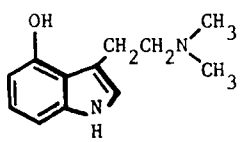
SUMMARY

^{14}C- and ^{3}H-Labelled psilocin (4-hydroxy-N,N-dimethyltryptamine), the principal, active agent of hallucinogenic mushrooms, was synthesized from 2-methyl-3-nitrophenol *via* 4-benzyloxyindole. ^{14}C-Labelled potassium cyanide was reacted with 4-benzyloxygramine (obtained from 4-benzyloxyindole) to give ^{14}C-4-benzyloxy-3-indole acetic acid, an intermediate for ^{14}C-psilocin synthesis. ^{3}H-Labelled lithium aluminium hydride was used to react with 4-benzyloxy-3-indole-N,N-dimethylglyoxylamide (obtained from 4-benzyloxyindole) to give ^{3}H-4-benzyloxy-psilocin which was debenzylated to form ^{3}H-psilocin.

Key Words: Psilocin, hallucinogenic mushrooms, psychedelic drug.

INTRODUCTION

Psilocin (4-hydroxy-N,N-dimethyltryptamine) (1) is a principal, active chemical of hallucinogenic mushrooms[1] which are widely self-administered by man as a psychedelic drug in the Pacific Northwest of North America and many parts of Central America.



(1)

There is a paucity of information on the chemical synthesis of psilocin. Unlabelled psilocin was first prepared chemically by Stoll *et al.*[2] according to Scheme I:

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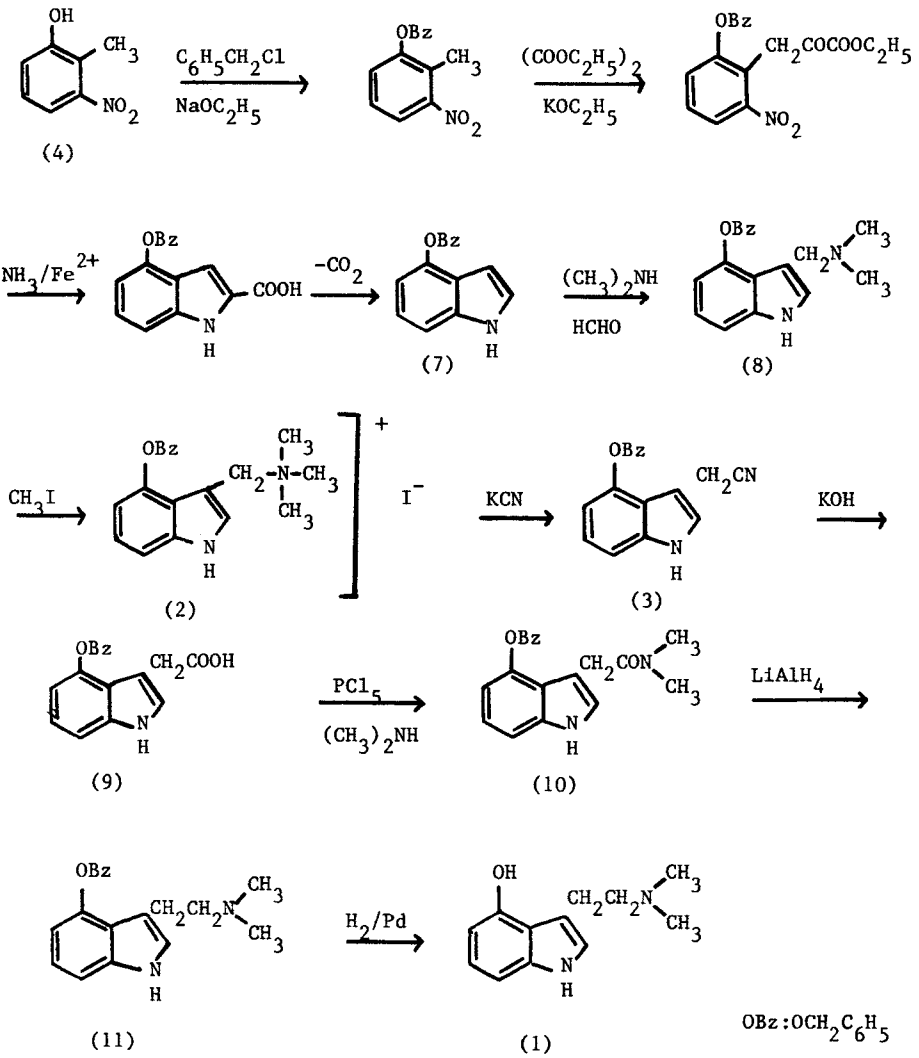


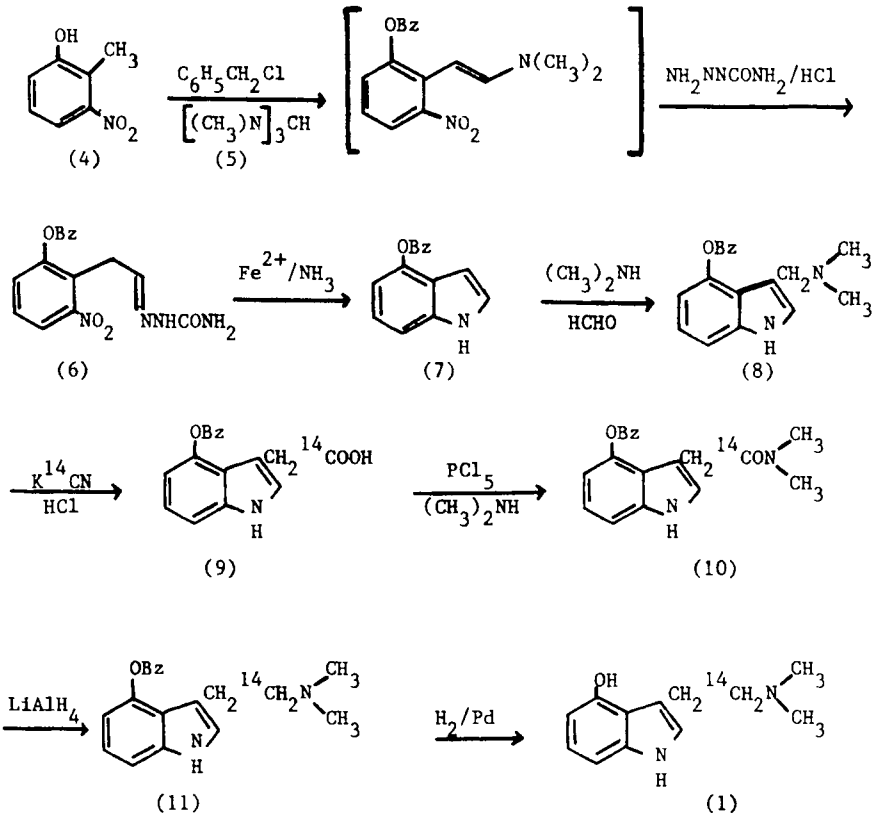
SCHEME I

^{14}C-Labelled psilocin was prepared by Kalberer et al.[3] with a similar scheme. They treated 4-benzyloxygramine-methiodide (2) with K^{14}CN to form ^{14}C-4-benzyloxy-3-indoleacetonitrile (3), an intermediate of ^{14}C-psilocin synthesis. The major drawbacks of Scheme I include the many synthetic steps and the difficulty of obtaining a sufficient amount of intermediate (2) to carry out the next reaction.

This communication describes an improved method for ^{14}C-psilocin synthesis and a procedure for ^{3}H-psilocin preparation.

RESULTS AND DISCUSSION

Synthesis of ^{14}C-labelled psilocin was accomplished by Scheme II:



OBz:$OCH_2C_6H_5$

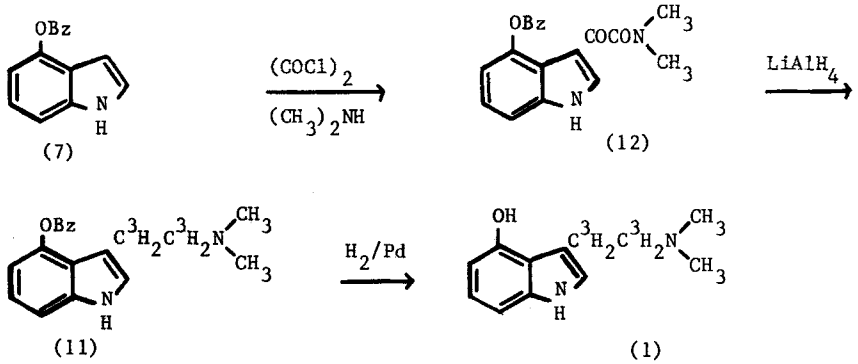
SCHEME II

The first stage of this synthesis involved the reaction of 2-methyl-3-nitrophenol (4) with tris(dimethylamino)methane (5). The product thus formed (not isolated) was treated with semicarbazide hydrochloride to give the semicarbazone (6), as described by Kruse[4]. Cyclization of (6) with ammoniacal ferrous sulphate achieved the 4-benzyloxyindole (7). Treatment of

(7) with dimethylamine gave 4-benzyloxygramine (8) which when refluxed with $K^{14}CN$ over a period of 80 hr, followed by acidification of the solution, immediately yielded ^{14}C-4-benzyloxy-3-indole acetic acid (9). Treatment of (9) with phosphorus pentachloride and dimethylamine gave ^{14}C-4-benzyloxy-3-indole-dimethylacetamide (10). Reduction of (10) with lithium aluminium hydride followed by hydrogenation with palladium as a catalyst gave the required product ^{14}C-psilocin (1).

Chemical synthesis of ^{14}C-psilocin with Scheme II has at least two advantages over Scheme I: (a) Scheme II is shorter than Scheme I by three steps. Therefore, the overall reaction time required for ^{14}C-psilocin synthesis is greatly shortened. Scheme I requires the conversion of compound (8) to compound (2) and compound (3) to compound (9). Each of these reactions needs at least 24 hr. These reactions are not required by Scheme II. (b) The overall yield of ^{14}C-psilocin is greatly increased because of improved yields of the intermediates. In our laboratory, the yield of compound (7) is about 45% by Scheme II as compared to <10% by Scheme I. We also have <10% yield in converting compound (2) to compound (3) by Scheme I, although Stoll et al.[2] and Kalberer et al.[3] have reported higher yields for this step.

Synthesis of ^{3}H-psilocin was accomplished by Scheme III as described by Masako et al.[5].



SCHEME III

Compound (7) was first treated with oxalyl chloride at 5-10°C for 1 hr and then with dimethylamine at room temperature for a further 30 min. The product thus formed (12) was reduced by ^{3}H-$LiAlCH_4$ and subsequent debenzylation afforded the required ^{3}H-psilocin.

The synthesis of ^{3}H-labelled psilocin is more simple than ^{14}C-labelled psilocin because only three steps are involved from the intermediate benzyloxyindole (7) to psilocin and all the steps are in reasonably good yields.

EXPERIMENTAL

I. ^{14}C-PSILOCIN

6-Benzyloxy-2-nitro-phenylacetaldehyde semicarbazone (6)

A 500 ml flask equipped with a reflux condenser was flushed with N_2 and charged with 50% sodium hydride dispersion (4.8 g, 0.1 m). This dispersion was washed with hexane (2 x 50 ml), then suspended in dry dimethylformamide (50 ml) during the slow addition of 2-methyl-3-nitrophenol (4) (16 g, 0.1 m). The red solution was cooled, and benzyl chloride (12.3 g, 0.11 m) was added rapidly. The solution was kept at 90°C for 20 min. Tris(dimethylamino)methane (5) (21.75 g, 0.15 m) was added followed by further heating at 115°C for 3 hr. The mixture was cooled and a solution of semicarbazide hydrochloride (11.7 g, 0.1 m) and concentrated HCl (9 ml, 0.1 m) in water (125 ml) was added. The mixture was cooled and filtered. The precipitate was washed sequentially with water (100 ml), ice-cold ethanol (150 ml) and ether (150 ml), then dried to give 25.2 g (77%) of compound (6), with mp 185-188°C (lit. 188-190°C[5]); mass spect. (C.I.) M/Z 329 $(M+1)^+$.

4-Benzyloxyindole (7)

A mixture of the semicarbazone (6) (11.5 g, 0.03 m) in ethanol (40 ml), ammonia (48 ml) and water (20 ml) was stirred as a mixture of ferrous sulphate (63 g, 0.26 m) and boiling water (75 ml) was added. After boiling for 1 hr, ethanol was removed in vacuo. The mixture was then filtered. Boiling ethyl acetate (100 ml) was used for the extraction and wash of the black precipitate.

The combined ethyl acetate extracts were dried and evaporated to give 8.5 g of black product. The crude product was purified by passing it through a silica gel column, using $CHCl_3$ as the eluting solvent. Removal of the solvent gave 4.3g (58% yield), of pure 4-benzyloxyindole, with mp 69-71°C (lit. 70-71°C)[4]; mass spect. (E.I.) M/Z 223 (M^+).

4-Benzyloxygramine (8)

A cooled solution of 25% dimethylamine (4.25 ml, 0.024 m) was added to a solution of cold 37% formaldehyde (1.72g, 0.021 m) in acetic acid (3g). The 4-benzyloxyindole (7) (4.46 g, 0.02 m) was added to the ice-cooled mixture and was kept at 37°C overnight. At the end of the reaction, NaOH (4 g) in water (30 ml) was added with vigorous stirring. The white precipitate formed was filtered and recrystallised from acetone:hexane (3:2, v/v) to give 5.52 g (72.5% yield) of compound (8). Mass spect. (C.I) M/Z 281, $(M+1)^+$. Microanalysis calc. for $C_{18}H_{20}N_2O$ C:77.11; H:7.19; N:9.99%. Found for C:77.09; H:7.32; N:9.9%.

^{14}C-4-Benzyloxy-3-indole-acetic acid (9)

The $K^{14}CN$ (1.2 mg, 54 mCi $mmol^{-1}$) and unlabelled KCN (2.32 g, 0.035 m) were dissolved in water (5 ml) and were refluxed with 4-benzyloxygramine (8) (1.95 g, 7.14×10^{-3} m) in ethanol (15 ml) for 80 hr. At the end of the reaction, water (10 ml) was added and the solution was filtered and concentrated to about 15 ml under reduced pressure. The mixture was cooled and the precipitate was filtered. To the filtrate, conc. HCl was added at 5-10°C, until the solution reached a pH of 1-2. The product was filtered and dried under vacuum. The yield of compound (9) is 0.92 g (46%) and the mass spect. (E.I.) M/Z 281 (M^+). It was used for the next preparation without further purification.

^{14}C-4-Benzyloxy-3-indole-N,N-dimethylacetamide (10)

The crude acid (518 mg, 1.85×10^{-3} m) was suspended in anhydrous ether (25 ml) and stirred at 0°C with phosphorus pentachloride (600 mg) until a clear solution was obtained. This solution was cooled while a 10% solution of dimethylamine in anhydrous ether (30 ml) was added. The mixture was stirred for 30 min. At the end of the reaction, the solution was neutralised with saturated

$NaHCO_3$ and the product was extracted with chloroform (3x30 ml). After removal of the solvent, the residue was crystallised from benzene. The yield of compound (10) was 340 mg (60%).

^{14}C-4-Benzyloxy-N,N-dimethyltryptamine (11)

The amide (10) was dissolved in anhydrous THF and the solution was added with stirring and cooling to $LiAlH_4$ (100 mg) suspended in THF (10 ml). The mixture was stirred for 3 hr at 0°C. Excess $LiAlH_4$ was cautiously removed with water. 20% NaOH was added and the reduction product was extracted with ether, and recrystallised from ether/pet. ether (bp 40-60°C). The yield of compound (11) is 280 mg, (87%).

^{14}C-Psilocin (1)

A slow stream of hydrogen was bubbled through a solution of compound (11) dissolved in ethanol (30 ml) in the presence of palladium catalyst (10% charcoal, 25 mg). The reaction was stirred for 7 hr at room temperature and pressure. The catalyst was filtered off and, the filtrate was concentrated to a few millilitres. The product was purified by preparative TLC plate, using water:acetic acid:butan-1-ol (5:1:4) as the eluting solvent. ^{14}C-psilocin was extracted from the plate with anhydrous ethanol (3x75 ml). Evaporation of the solvent gave 155 mg of compound (1) (80% yield) with specific activity of 52 µCi $mmol^{-1}$.

II.^{3}H-PSILOCIN

4-Benzyloxy-3-indole-N,N-dimethylglyoxyamide (12)

To a solution of compound (7) (0.5 g, 2.24 $x10^{-3}$m) in anhydrous ether was added oxalyl chloride (0.5 ml, $6x10^{-3}$ m) with sufficient stirring at 0°C and the mixture was stirred at 5-10°C for an additional 1 hr.

After cooling, the mixture was treated with dimethylamine (1 g in 10 ml anhydrous ether) and stirred at room temperature for 30 min. The precipitate formed was filtered and washed with ether. The product was dried under reduced pressure and was dissolved in a hot benzene/methanol solution. After cooling, pet. ether (bp 60°-80°C) was added to give compound (12) 510 mg in 71% yield. Mass spect. (C.I.) M/Z 323 $(M+1)^+$.

^{3}H-4-Benzyloxy-N,N-dimethyltryptamine (11)

To a solution of compound (12) (100 mg, 3.1×10^{-4} m) in anhydrous THF (15 ml) was added ^{3}H-$LiAlH_4$(0.5 mg, 437 mCi $mmol^{-1}$) and unlabelled $LiAlH_4$ (100 mg, 2.6×10^{-3} m) in THF (10 ml) with stirring. The mixture was refluxed for 3 hr. After standing overnight, the reaction mixture was cooled and the excess $LiAlH_4$ was decomposed with methanol. To the solution was added saturated Na_2SO_4 (3 ml) and the precipitate formed was removed by filtration. To the filtrate, 5% tartaric acid was added (20 ml), and the by product was isolated with ether (3x40 ml). The solution was neutralised with 4N NaOH and the product was extracted with chloroform (3x50 ml). After evaporation of the solvent, the residue was treated with pet. ether (bp 40°- 60°C) and gave the product of (11) in 60 mg (67%) yield. Mass spect. (C.I.) M/Z 295 $(M+1)^{+}$.

^{3}H-4-Hydroxy-N,N-dimethyltryptamine (Psilocin(1))

The compound (11) (60 mg) was treated with palladium and hydrogen as described previously. The yield was 25 mg (60%) and the specific activity was 12 μCi $mmol^{-1}$.

Acknowledgement

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