SYNTHESIS OF PHENCYCLIDINE AND ITS ANALOGUES LABELED WITH ^{14}C AND ^{3}H

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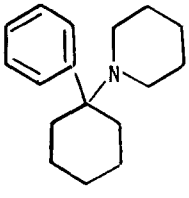
SUMMARY

^{14}C-Labeled phencyclidine, piperidinocyclohexane carbonitrile and phenylcyclohexene were synthesized chemically from ^{14}C-labeled bromobenzene or cyclohexanone. ^{3}H-Labeled N-ethyl-1-phenylcyclohexylamine was prepared by reducing N-acetyl-1-phenylcyclohexylamine with ^{3}H-lithium aluminum hydride.

Key Words: Phencyclidine, piperidinocyclohexane carbonitrile, phenylcyclohexene, N-ethyl-1-phenylcyclohexylamine

INTRODUCTION

Phencyclidine (1-(1-phenylcyclohexyl) piperidine) (1) was introduced by Parke-Davis Co. as an intravenous anesthetic[1] and has had limited use in clinical medicine due to its psychotomimetic and convulsant side effects. Comppund 1 is used as an animal tranquilizer and is widely self-administered by man as a psychedelic drug. Illicit samples of compound 1 frequently contain piperidinocyclohexane carbonitrile (2), a synthetic intermediate of compound 1, as a contaminant[2].



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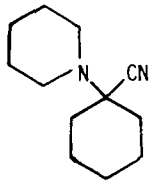

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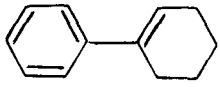
Compound 1 is abused by humans mainly orally or by smoke inhalation. About 35-50% of compound 1 smoked is decomposed to phenylcyclohexene (3)[3]. There are at least 30 known chemically similar analogues of compound 1. Some of these analogues such as N-ethyl-1-phenylcyclohexylamine (4) have been identified in street drug samples[4].



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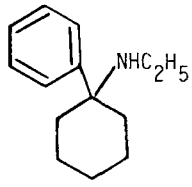

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In order to investigate the metabolic fates and potential toxicities of these compounds, we have prepared ^{14}C-labeled compounds 1, 2 and 3 and ^{3}H-labeled 4.

RESULTS AND DISCUSSION

The syntheses of ^{14}C-labeled 1 and 2 were accomplished by the procedure described by Maddox et al.[5] (Fig. 1) except that the proportions of the reactants were varied considerably. The products were used without further purification.

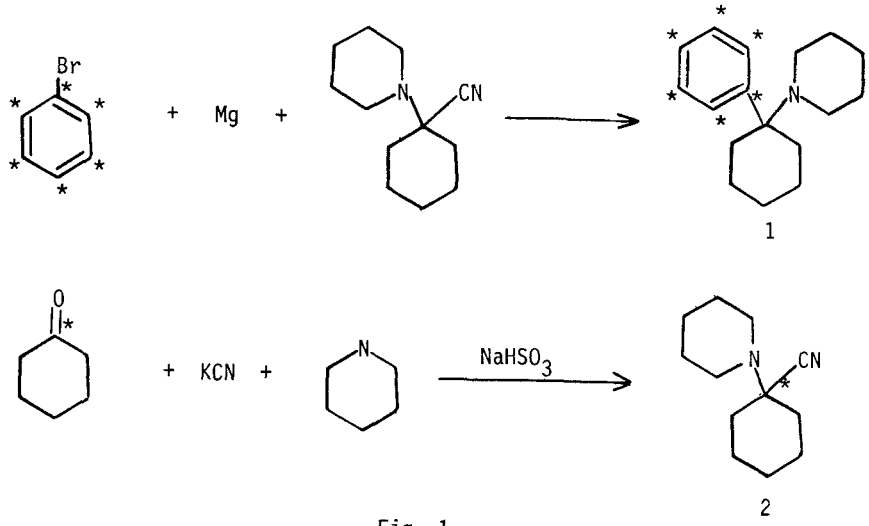

Fig. 1.

^{14}C-Labeled 3 was prepared by acid hydrolysis of the Grignard reaction product of cyclohexanone and ^{14}C-bromobenzene (Fig. 2), and was purified by preparative thin layer chromatography.

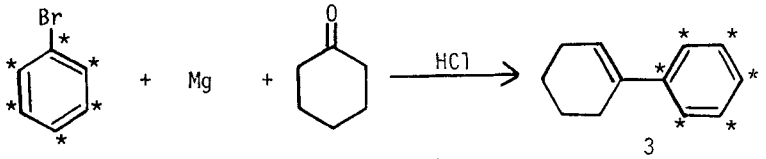

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Fig. 2.

There are two possible routes to synthesize compound 4: (a) Maddox et al.[5] reported 50% yield of compound 4 by reacting bromobenzene with N-cyclohexylidene ethylamine in the presence of lithium. In our laboratory, however, the yield was 13%, probably due to the low sodium content of modern lithium. (b) Bailey[4] also reported chemical synthesis by reducing N-acetyl-1-phenylcyclohexylamine with lithium aluminum hydride. He prepared the intermediate by acetylation of 1-phenylcyclohexylamine. We improved the synthesis of the intermediate by the Ritter reaction using 1-phenylcyclohexene and acetonitrile. ^{3}H-Labeled 4 was synthesized by reducing the intermediate with ^{3}H-lithium aluminum hydride (Fig. 3).

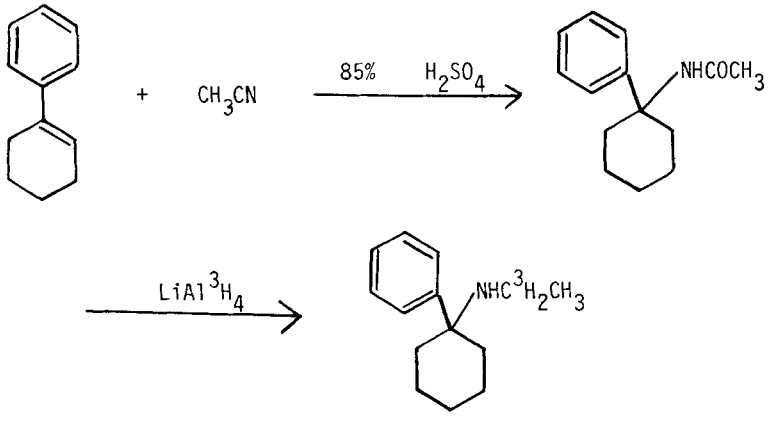

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Fig. 3.

The experimental conditions for the preparation of ^{14}C-labeled compounds 1, 2 and 3 and ^{3}H-labeled 4 were optimized several times using nonradioactive materials. The final products from these preliminary syntheses were characterized by melting points and/or cochromatography (thin-layer and gas chromatography). The melting points of the hydrochlorides of 1 and 4 were, respectively, 218-220°C and 229-231°C. The melting point range of 2 was measured to be 64-67°C.

Radiochemical purities of compounds 1, 2, 3 and 4 were respectively greater than 99%, 97%, 96% and 99%. Proof of radiochemical purity was shown using thin layer chromatography and autoradiography.

EXPERIMENTAL

1-(1-^{14}C-phenyl cyclohexyl) piperidine, (*1*).

Magnesium (28.6 mg, 1.17 mmol) and ether (2 ml) were placed in a three-necked, 50-ml round bottom flask fitted with a gas inlet tube, a reflux condenser protected by a $CaCl_2$ tube, and a dropping funnel. ^{14}C-Labeled bromobenzene (2.8 mg, 57 mCi/mmol) from New England Nuclear Cooperation was diluted with inactive bromobenzene carrier (170 mg, 1.09 mmol) and ether (2 ml), and the mixture was added drop by drop into the flask. The reaction mixture was refluxed for 30 min. An ethereal solution (3 ml) of unlabeled 2 (271 mg, 1.41 mmol) was added slowly to the mixture, producing a white precipitate. After being refluxed for an additional h, the mixture was hydrolysed with 4N hydrobromic acid and then extracted first with ether and then with isooctane. The remaining aqueous layer was basified with potassium carbonate and extracted with a mixture of ether/isooctane (50:50) twice. The organic layer was dried with anhydrous sulfate and evaporated to dryness. The residue was redissolved in ether (5 ml). Precipitate resulted when hydrogen chloride gas was bubbled through the solution. This precipitate was collected by filtration and dried under vacuum. The product weighed 0.17 g (0.58 mmol), yield 54%. Mass spectrometric[6] and chromatographic[7] analyses showed the products to be pure with

specific activities ranging between 0.58 to 0.89 mCi/mmol.

1-Piperidino-(^{14}*C-cyclohexyl) carbonitrile*, (2).

^{14}C-Cyclohexanone (1.17 mg, 8.4 mCi/mmol) diluted with inactive carrier cyclohexanone (3.15 mg, 0.03 mmol) was mixed with an aqueous solution (0.1 ml) of sodium bisulfite (4.78 mg, 0.05 mmol) at 0°C with a magnetic stirrer. An aqueous solution (0.04 ml) of potassium cyanide (5.46 mg, 0.084 mmol) and piperidine (8.5 mg, 0.10 mmol) was then added to the stirring, cold slurry. The mixture was left to react overnight. The product, a white precipitate, was isolated by filtration and dried in a vacuum dessicator. The product weighed 3.87 mg (0.02 mmol), yield 48%. Chromatographic analyses[8] showed that the products were pure, with specific activities ranging between 1.5 to 2.5 mCi/mmol.

1-^{14}*C-Phenylcyclohexene*, (3).

^{14}C-Bromobenzene (1.57 mg, 25 mCi/mmol) diluted with inactive carrier bromobenzene (47 mg, 0.30 mmol) and ether (2 ml) was added drop by drop to a 50-ml three-necked round bottom flask containing magnesium (22 mg, 0.91 mmol) and ether (3 ml) under nitrogen. An ethereal solution of cyclohexanone (66 mg, 0.67 mmol) was then added to the refluxing solution of ^{14}C-phenylmagnesium bromide. The reaction mixture was hydrolysed by refluxing with concentrated HCl (2 ml) for 0.5 h.

After cooling to room temperature, the reaction mixture was extracted with ether (15 ml) twice. The ethereal extracts were combined, dried with anhydrous sodium sulfate and evaporated down to a residual yellow oil. The radiochemical purity of the crude product was 85%.

To obtain a purer product, the yellow oil was redissolved in ether (0.5 ml) and streaked on a preparative thin-layer plate (Silica gel 60 F-265, E. Merck Co.), which was developed in hexane. The product migrated to give a discrete region that was easily distinguished under UV illumination and had an R_f value identical to the authentic material purchased from Aldrich Chemical Co. The area of the plate containing the pure product was scraped and exhaustively

extracted with chloroform. The product weighed 3.55 mg (0.023 mmol), yield 7%, and had a radiochemical purity of 95% with a specific activity of 3.77 mCi/mmol.

N-(^{3}*H-ethyl)-1-phenylcyclohexylamine,* (4).

Cooled 85% sulphuric acid (54 g) was added slowly to 1-phenylcyclohexene (13 g, 82.1 mmol) in acetonitrile (125 ml). The mixture was stirred for 24 h and poured onto a mixture of ice and water. The mixture was extracted twice with ether (30 ml). The ether layer was separated from the aqueous layer, combined and extracted by 1N NaOH (100 ml). The ether layer was then separated and the remaining aqueous layer was washed by fresh ether. The ether extracts were combined, dried with anhydrous sodium sulfate and reduced in volume. When petroleum ether (b.p. 35-60°C) was added in equal volume to the ethereal solution, 3.15 g (18%) of N-acetyl-1-phenylcyclohexylamine crystalized. The crude product could be used for further synthesis without purification.

N-Acetyl-1-phenylcyclohexylamine (150 mg, 0.69 mmol) was dissolved in dry tetrahydrofuran (20 ml). ^{3}H-Lithium aluminum hydride (75.2 mg, 100 mCi/mmol) was then added to the solution. The mixture was refluxed for one week. After adding 5% NaOH to decompose excess lithium aluminum hydride, the mixture was extracted twice with ether. The ether extracts were combined and evaporated to dryness. The oily residue was redissolved in ether (1.5 ml) and hydrogen chloride gas was bubbled through the ethereal solution. After ether was evaporated away, the oily residue was redissolved in 0.4 ml of a mixture of isopropanol/ether (3:1). After the solution stood overnight at 0°C, crystals began to appear. Excess solvent was decanted and the crystals were washed with ether. The product weighed 124 mg (0.61 mmol), yield 88%, with a specific activity of 5.49 mCi/mmol. The radiochemical purity of the product was better than 99% as determined by thin-layer chromatography (Silica gel G in acetone/ammonia, 99:1).

REFERENCES

1. Chen G., Ensor C.R., Russell D. and Bohner B. - J. Pharmacol. Exp. Ther. 127:241 (1959).
2. Kalir A., Edery, H., Pelah Z., Balderman D. and Porath G. - J. Med. Chem. 12:473 (1969).
3. Martin B.R., Freeman A.S., Kelly K.L., Clayton V.M., Vincek W.C. and Harris L.S. - Fed. Proc. 39:302 (1980).
4. Bailey K. - J. Pharm. Sci. 67:885 (1978).
5. Maddox V.H., Godefroi E.F. and Parcell R.F. - J. Med. Chem. 8:230 (1965).
6. Law, F.C.P. and Farquharson, T.E. - In Microsomes, Drug Metabolism and Chemical Carcinogenesis. Academic Press, New York, 1980, p. 985.
7. Law, F.C.P. - Toxicol. Appl. Pharmacol. 57:263 (1981).
8. Law, F.C.P. - Res. Comm. Subst. Abuse 1:273 (1980).