A RAPID SYNTHESIS OF NITROGEN-13 LABELLED AMPHETAMINE

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SUMMARY

The preparation of nitrogen-13 labelled α-methylphenyl-ethylamine (amphetamine), utilizing a sealed reaction system is described.

Key Words: Nitrogen-13, amphetamine, radiocontaminants.

INTRODUCTION

The clinical interest (1-3) in compounds structurally related to amphetamine as well as the potential of being able to describe at a physiological-biochemical level the mechanism of action of this sympathomimetic stimulant prompted our investigation into rapid synthetic methods for the preparation of nitrogen-13 labelled α-methyl-phenylethylamine.

Nitrogen-13 is a short-lived radioisotope of nitrogen well suited to a tracer role in biomedical applications. Although its short half-life ($t_{\frac{1}{2}}$ = 9.96 m) imposes limits on the chemical reaction sequences, a number of complex compounds

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have been labelled by utilizing rapid efficient syntheses (4-8). Nitrogen-13 decays by positron emission with a β^+ end point of 1.98 MeV (9). The positron can be directly detected or the nuclide may be assayed by utilizing the two 511 keV photons created by annihilation of the positron.

Production of Radionuclide

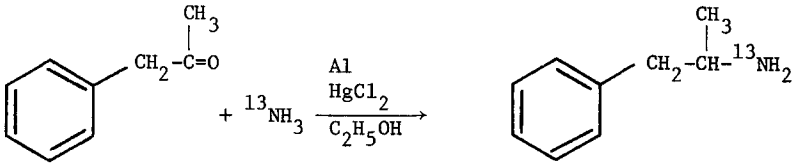
The number of nuclear reactions which result in the production of nitrogen-13 is large indeed; however, the most commonly employed reactions are: $C^{12}(d,n)N^{13}$, $O^{16}(p,\alpha)N^{13}$. The chemical porducts, resulting from the interaction of nitrogen-13 atoms produced via the $^{16}O(p,\alpha)^{13}N$ nuclear reaction with 18 MeV protons on a water target or alternatively, oxygen gas target, are believed to be a complex function of radiation chemistry and hot atom chemistry (11-15). Both target systems lead to the formation of nitrogen-13 labelled oxides of nitrogen, which are readily reduced to labelled ammonia (4,10).

Using principally water as the target material for the proton reaction and a modification of the reduction procedure reported by Vaalburg (10) the synthesis of the nitrogen-13 labelled α-methyl-phenylethylamine was achieved. Following a 25 μA-min irradiation, the radioactive water was introduced into a reduction flask containing 200 mg Devarda's alloy (Baker Chemical Co., Phillipsburg, NJ) and 4 g of sodium hydroxide. The radiolabelled ammonia was distilled in a stream of nitrogen and collected in 1 milliliter of ethanol containing 0.04 ml of phenyl acetone.

Trace radiocontaminants present in the water, such as fluorine-18 ($t_{\frac{1}{2}}$ = 109.7 m), carbon-11 ($t_{\frac{1}{2}}$ = 20.4 m) and vanadium-48 ($t_{\frac{1}{2}}$ = 16.0 d), are not distilled with the nitrogen-13 product, as confirmed by gamma ray spectroscopy utilizing a Ge(Li) detector.

EXPERIMENTAL

The facile synthesis of amphetamine (16) has been modified for the synthesis of the labelled amphetamine as illustrated in Figure 1.



The mixture of nitrogen-13 labelled ammonia and phenylacetone was introduced into an aluminum reaction bomb (2 cc volume) along with 0.2 ml concentrated ammonium hydroxide, 100 mg aluminum (10 mesh and finer) and 1 mg mercuric chloride. The sealed vessel was heated on a hot plate at 100°C for 15 minutes, followed by immediate cooling of the vessel in ice water. The contents were added to 1 ml of ice water, the solution made alkaline (pH > 9) with 0.5 g potassium hydroxide, and extracted with diethyl ether. The extractions are treated with 3 N hydrochloric acid, the resulting aqueous layer made alkaline and extracted with diethyl ether, the ether dried over sodium sulfate and finally the solvent removed in vacuo.

The chemical integrity of the nitrogen-13 labelled compound was confirmed by thin layer chromatography (silica gel) in two solvent systems, i.e. chloroform and ethanolammonium hydroxide (99:1). All the activity was congruent with the amphetamine standard. Radiochemical yields are nearly 3.5% based on the labelled ammonium hydroxide used. The synthesis was performed on a larger scale, which allowed the determination of the index of refraction (n_D^{26} = 1.518) in agreement (17) with the standard, as well as nuclear magnetic resonance analysis of the vacuum distilled product. The chemical yield based on phenyl acetone was 30%. Thus, with 100 mCi of ^{13}N labelled ammonia available as reactant, ^{13}N labelled α-methyl-phenylethylamine SA ∿ 8 mCi/mmole is readily obtained for experimental studies. It is important to point out that an excess of ammonia is required in order to avoid the formation of the secondary amine.

DISCUSSION AND CONCLUSION

Renewed interest in amphetamine and structurally related drugs caused us to investigate the possibility of developing a rapid synthetic procedure for

labelling this compound. It is hoped that the preparation of radiopharmaceuticals such as the amphetamine will allow doses below the pharmacological activity threshold such that elucidation of metabolic pathways and resolution of species differences in metabolism may be understood. The main disadvantage of the one-step procedure for clinical application is the low specific activity of the final product due to the necessity of adding carrier amounts of ammonia.

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