THE PREPARATION OF ^{15}N-PHENOXYBENZAMINE

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Received on February 19, 1975.

SUMMARY

Phenoxybenzamine [N-Benzyl-N-(1-phenoxyisopropyl)-2-chloroethylamine hydrochloride] has been labelled with Nitrogen-15 by a direct synthesis from ^{15}*N-ammonium chloride. The isotopic enrichment was 92.8%.*

Introduction

We have communicated the preparation of ^{14}C-phenoxybenzamine (Ib)[1] as well as ^{3}H-phenoxybenzamine (Ic).[2] We now report the preparation of ^{15}N-phenoxybenzamine (Ia) with isotopic enrichment of 92.8% for mass spectral studies.[6]

The key intermediate, ^{15}N-ethanolamine (III) was prepared by a Gabriel synthesis. ^{15}N-Phthalimide, derived from ^{15}N-ammonium chloride (96% isotopic enrichment) was condensed with ethylene carbonate[3] to give II in 66% yield. The phtholyl group was removed by alkaline hydrolysis and ethanolamine isolated as the hydrochloride salt. Subsequent neutralization and distillation gave ^{15}N-ethanolamine in 34% yield from ^{15}N-ammonium chloride.

Alkylation of ^{15}N-ethanolamine was carried out neat in phenoxyisopropyl chloride with sodium carbonate as the acid scavenger. The yields of IV ranged from 30-67%; low yields were attributed to residual alcohol or water in the ethanolamine. Reaction of IV with benzyl chloride proceeded in nearly quantitative yield to the tertiary amine V. Chlorination was carried out in the usual manner and gave ^{15}N-phenoxybenzamine in a 48% yield from IV.

Experimental[5]

^{15}N-Phthalimide

A solution of $^{15}NH_4Cl$ (5.0 g, 92 mM; 96% isotopic enrichment) in 5 ml water in a 25 ml gas generator was treated dropwise with sodium hydroxide (7 ml, 50%) and the ammonia passed into the bottom of a receiving flask containing a stirred suspension of phthalic acid (15.8 g, 95 mM) in 40 ml of water. The generating flask was heated and the final gas transfer aided by a slow stream of argon.

The phthalate solution was distilled to dryness with periodic mixing until a solid was observed subliming from the flask. The diminution of carboxylate ion (ir 1550 cm^{-1}) indicated nearly complete reaction. The solid was collected with the aid of an ethanol/ether wash. Yield 11.54 g, 78 mM, 85%.

^{15}N-2-Hydroxyethyl Phthalide (II)

^{15}N-Phthalimide (11.54 g, 77.9 mM) was heated at 200° with ethylene carbonate (8.8 g, 100 mM).[3] After two hours the solution was cooled, and treated with 150 ml of boiling water. The hot solution was treated with darco and filtered. The resulting white solid was collected and dried at 50° (10.0 g, 52 mM, 66%). Melting point, 115-120° (reported 122-126°).[4]

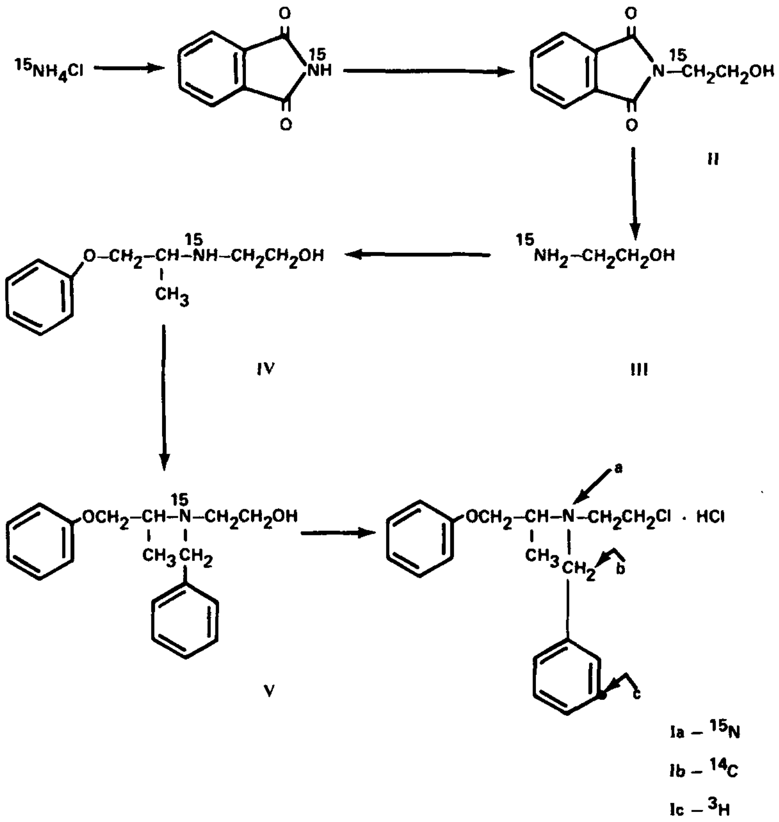
^{15}N-Ethanolamine Hydrochloride

^{15}N-2-Hydroxyethyl phthalide (10.0 g, 52 mm), potassium hydroxide (10 g) and 20 ml of water were refluxed for 10 hrs. The solution was distilled into an excess of 3N hydrochloric acid cooled in a dry ice bath. The distillation was complete at 15 mm. The aqueous distillate was brought to pH 2 with concentrated hydrochloric acid. This solution was stripped to an oil on the rotary evaporator using ethanol/benzene chaser. The evaporation was repeated until the product solidified on the addition of ether. Hygroscopic solid (5.0 g, 51 mM).

^{15}N-Ethanolamine (III)

An intimate mixture of sodium methoxide (2.84 g, 52.6 mM) and the

Synthetic Route



above salt (5.0 g) was distilled at a bath temperature of 110°. After methanol was no longer collected, the product was distilled at 90-130° (bath) and 15 mm into a receiver cooled to -70°. The product weighed 2.29 g. The high resolution mass spectrum showed an isotopic enrichment of 92.6% but disclosed the presence of water and methanol (ca. 15%). The yield from ^{15}N-ammonium chloride was 34% (corrected).

^{15}N-Phenoxyisopropyl Ethanolamine (IV)

^{15}N-Ethanolamine (2.2 g, 36 mM), phenoxyisopropyl chloride (15 ml) and sodium carbonate (5.7 g, 54 mM) were heated at 190° (bath temperature) for 4 hrs. The reaction was quenched with water and extracted with chloroform. The chloroform was washed well with water and the product extracted from the chloroform with 5% hydrochloric acid. The acid solution was washed with chloroform and then the pH was adjusted to 10 with 2N sodium hydroxide. The free base was again extracted with chloroform, washed with water and dried (magnesium sulfate). Removal of solvent gave an oil which gave a white crystalline solid on trituration with hexane, mp 72-73°, yield 2.12 g (10.9 mM, 30%). When commercial ethanolamine was used the yields were 59 and 67%. The poor yield in the above case is attributed to the methanol or water that was present in the ^{15}N-ethanolamine.

^{15}N-Benzyl-N-(1-phenoxyisopropyl)-ethanolamine (V)

Amine IV (1.99 g, 10.2 mm), benzyl chloride (1.31 g, 10.4 mM), sodium bicarbonate (0.874 g, 10.4 mM) and ethanol (20 ml, formula 2B) were refluxed for 24 hrs. The inorganic salts were filtered and the alcohol removed on a rotary evaporator. The oily residue was dissolved in ether, dried (magnesium sulfate) and filtered. Concentration gave a quantitative yield of V; no purification necessary.

^{15}N-Benzyl-N-(1-phenoxyisopropyl)-2-chloroethylamine Hydrochloride (Ia)

The above tertiary amine (10.2 mM) was dissolved in dry chloroform (5 ml), and hydrogen chloride was bubbled through this solution (apparent pH 1-2 to wet litmus). The solution was cooled to 0° and a solution of thionyl chloride (1.21 g, 10.2 mM) in chloroform (5 ml) was added dropwise, and the reaction allowed to reach room temperature. The reaction was heated at 50-60° for two hours and the solvent removed. The resulting tan oil was triturated with ether to give a white solid, which was recrystallized twice from chloroform-ether, mp 136.5-138° (yield 1.1 g, 3.24 mM, 32%). From the mother liquors was isolated additional Ia of equal purity (thin layer chromatography on Silica Gel GF, R_f .85, heptane:chloroform:methanol - 50:35:15). The total yield 1.65 g, 48% from IV.

The following analysis was obtained.

UV λ max 263 nm (ε 565), .05N HCl in 75% ethanol.

Total Chloride, (theory 20.89) 20.40

Ionizable Chloride, (theory 10.45) 10.39

Non Aqueous Titration (Amine) 98.6%

Mass Spectrum (^{15}N content) 92.8%

Acknowledgements:

We are grateful to Mr. Alex Post and Mr. David Steiger of the Analytical and Physical Chemistry Section for our analytical results, and Mr. Gerald D. Roberts who determined the mass spectra.

We acknowledge Dr. Daniel R. Knapp of the Medical University of South Carolina, Department of Pharmacology, who encouraged this project and who provided the ^{15}N -ammonium chloride.

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