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NOTE

SYNTHESIS OF $[^{15}N]$-PROCAINE HYDROCHLORIDE

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S U M M A R Y

The synthesis of $[^{15}N]$- labelled procaine hydrochloride, using $(^{15}NH_4)_2SO_4$ as starting isotopically labelled material, is presented. The experimental procedure is an adaptation of the synthesis methods for the corresponding unlabelled compounds.

KEY WORDS: $[^{15}N]$ - procaine hydrochloride, synthesis, $[^{15}N]$ - ethanolamine, $[^{15}N]$ - β - diethylaminoethanol, condensation, p - aminobenzoic acid.

I N T R O D U C T I O N

The Romanian drugs Gerovital H_3 and Aslavital contain purposely stabilized procaine as active principle. Clinical studies have shown that these drugs present anabolic and entrophic effects, revitalize tissues, restore physical and intellectual resources of aged persons and have positive effects in the treatment of arthrytis, senility and depression (1 - 4).

The investigations performed "in vitro" on tissues of young as well as adult Wistar rats (liver and brain) have led to

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the conclusion that procaine from Gerovital H_3 and Aslavital is more persistent than procaine hydrochloride alone. Procaine seems to be more rapidly metabolized in the liver but very slowly in the brain. The age also influences the dynamics of procaine metabolism.

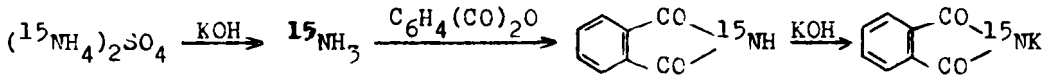
Mass spectrometry and especially mass spectrometry combined with gas chromatography (GC/MS), have been increasingly used in the last years in the pharmacokinetic investigation of drugs (7). The GC/MS analytical methods were employed due to high sensitivity in the ng/ml range and the specificity given by the use of the characteristic ions (8) from the mass spectrum of procaine.

Due to the fact that specifically deuterated procaine hydrochloride (5) and ^{14}C labelled compound (6) are not suitable for our experiments, we are obliged to utilise ^{15}N procaine hydrochloride, the synthesis of which is presented in this paper.

Quantitative analysis was performed with ^{15}N procaine hydrochloride as internal standard, or using the method of isotopic dillution.

E X P E R I M E N T A L

Synthesis of Potassium $[^{15}N]$ Phthalimide



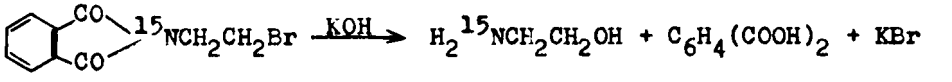
$[^{15}N]$ Phthalimide was prepared as described by Murray and Williams (9). Starting from 4.84 g ammonium sulphate (50 atom % ^{15}N), the yield of $[^{15}N]$ phthalimide was 5.18 g (96%).

The potassium salt of $[^{15}N]$phthalimide was prepared in 92% yield as described by Salzberg and Supniewski (10).

Synthesis of [^{15}N] - (2 - Bromoethyl) Phthalimide

[^{15}N] Bromoethylphthalimide was prepared as described (10). Starting from 6 g potassium [^{15}N] phthalimide and 18 g ethylene dibromide, the yield of bromoethylphthalimide was 7.43 g or 75%. The compound was used without further purification.

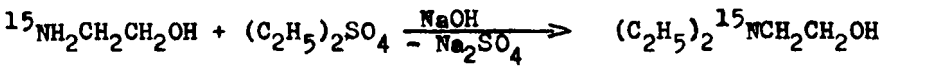
Synthesis of [^{15}N] Ethanolamine



[^{15}N] Bromoethylphthalimide was subjected to alkaline hydrolysis with 30% KOH (11).

Thus, 7.43 g bromoethylphthalimide with 9.27 g KOH in 37 ml water were heated until dissolved and then distilled to dryness. The dry residue was treated with 10 ml of water and distilled, off. This was repeated once more. The joint distillate, containing the ethanolamine, was freed from water by distillation at normal pressure (the aminoalcohol is not volatile with steam) first with dephlegmator at 100° and then without at 171 - 172°C. The yield of [^{15}N] ethanolamine was 1.42 g (80%).

Synthesis of [^{15}N] β - Diethylaminoethanol



β - Diethylaminoethanol was prepared as described. Ethanolamine (1.42 g) was heated for 50 minutes at 40° with an equimolar

amount of diethyl sulphate (3.6 g) and then treated with an equimolar amount of aqueous alkali. The diethylaminoethanol was separated by distillation under reduced pressure. To the aqueous solution was added benzene and the solution was distilled from a flask provided with a 50 cm column (packed with glass or carborundum). Distillation was continued until the temperature of the liquid reached 100° and that at the top of the column was 85°. The residue was transfered to a Claisen flask and distilled under reduced pressure (64° - 65°/18 mm). The total yield was 1.86 g (70%).

Synthesis of $[^{15}N]$ β - (Diethylamino) Chloroethane Hydrochloride

$$(C_2H_5)_2{}^{15}NCH_2CH_2OH \xrightarrow{SOCl_2} (C_2H_5)_2{}^{15}NCH_2CH_2Cl \cdot HCl$$

$[^{15}N]$ Diethylaminoethanol (1.86 g) in 12 ml benzene and few drops of dimethylformamide were cooled to 0° - 5° and then 1.5 ml of thionylchloride were added dropwise during 2 hrs. with stirring. Then the reaction mixture was warmed slowly and heated at reflux 1 hr. Benzene and excess of $SOCl_2$ were removed by distillation at atmospheric pressure. For complete removal of $SOCl_2$, to the mixture was added 3 ml benzene and the distillation continued under reduced pressure to dryness. The crude diethylaminochloroethane hydrochloride was dissolved in 20 ml isopropanol, treated with decolorising carbon, filtered, and the solution was cooled to 0 - 5°C. After crystallization, the product was filtered and dried in air, yielding 2.34 g product (85%).

Synthesis of $[^{15}N]$ - Procaine Hydrochloride

$$p - H_2N-[C_6H_4]COOH \xrightarrow{Na} p - H_2N-[C_6H_4]COONa \xrightarrow{ClC_2H_4{}^{15}N(C_2H_5)_2 \cdot HCl}$$

$$p\text{-}H_2N\text{-}\left[C_6H_4\right]COOC_2H_4{}^{15}N(C_2H_5)_2 \xrightarrow{HCl} \left[p\text{-}H_2N\text{-}C_6H_4COOC_2H_4{}^{15}NH(C_2H_5)_2\right]^{+}Cl^{-}$$

$\left[^{15}N\right]$ Procaine hydrochloride was prepared by condensation of p - aminobenzoic acid with (diethylamino)chloroethane hydrochloride, according to a Romanian Patent (12). The advantage of this method consists in the fact that the process proceeds in a single stage in isopropanol solution. First, the sodium salt of p - aminobenzoic acid, was prepared. In 38 ml isopropanol heated to reflux, there was added in small portions 0.62 g sodium and the reflux was continued until all sodium was consumed. This required about 1 hr. After the reaction mixture has been cooled to 40 - 50°, there was added 1.83 g p - aminobenzoic acid, followed by a reflux for 3 hrs. Then the reaction mixture was cooled to 6 - 10°, 2.34 g (diethylamino) chloroethane hydrochloride was added, and the mixture was stirred for 2 hrs. The reaction mixture was then stirred for about 2-3 hrs. at 50-70°. The sodium chloride was removed by filtration. The solution was cooled to 0-5° and with stirring, there was added dropwise isopropanol saturated with gaseous HCl until the pH reached 5-5.5. The product was collected by filtration, and washed with cold isopropanol. Crude $\left[^{15}N\right]$ Procaine hydrochloride is a light yellow solid. It was recrystallized from ethanol with decolorizing carbon yielding 3 g (85%) product, melting at 153-156°.

The labelled compound used as starting material $\left[^{15}N\right]$ ammonium sulfate was obtained from $H^{15}NO_3$ (99 atom% ^{15}N) produced in the Institute of Isotopic and Molecular Technology, 3400 Cluj-Napoca, 5, P.O. Box 700, Romania.

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