SYNTHESIS OF RADIOCARBON LABELLED LIDOCAINE (α-DIETHYLAMINOACET-[1-^{14}C]-2',6'-DIMETHYLANILIDE).

Mező I. and Teplán I.

Institute of Isotopes
Hungarian Academy of Sciences
Budapest, Hungary.

Received on October 21, 1971.

SUMMARY

Starting from sodium acetate-1-^{14}C, acetyl-1-^{14}C bromide was prepared and from this bromoacetyl-1-^{14}C bromide. The latter was used to acylate 2,6-dimetyl-aniline to α-bromoacet-(1-^{14}C)-2',6'-xylidide, with an activity yield of 31%. The labelled Lidocaine and its hydrochloride were prepared from this product by refluxing with diethylamine, with yields of 84.5% and 74.3%, respectively. The molar activity of the radiocarbon-labelled Lidocaine was found to be 3.48 mCi/mmole; thin-layer chromatography showed the product to be homogeneous.

Lidocaine (Xylicaine) is an extensively used local anaesthetic; its effect is quicker and stronger than that of Novocaine, yet it is less poisonous.

Lidocaine tritiated at random was first synthesized by GHANEM (1) and subsequently by GOSZTONYI (2), who used a modified version of the Wilzbach method. Lidocaine labelled with tritium at specific positions has been prepared from xylidine-4-^{3}H by MESHI (3) following the method of LÖFGREN and LUNDQUIST (4).

We have found no report dealing with the synthesis of radiocarbon-labelled Lidocaine. On the analogy of LÖFGREN and LUNDQUIST's method, we have used the synthesis scheme shown in Fig. 1. 2,6-Dimethylaniline was acylated with bromoacetyl-1-^{14}C bromide. It was found that the bromo-compound is much simpler to produce from sodium acetate-1-^{14}C than chloroacetyl-1-^{14}C chloride, as well as easier to handle and to store because of its higher boiling point. Acetyl-1-^{14}C bromide was prepared from sodium acetate by ANKER's method (5). This was then converted by ROPP's method (6) into bromoacetyl-1-^{14}C bromide which was used for the acylation of 2,6-dimethylaniline to α-bromoacet-(1-^{14}C)-2',6'-xylidide. The α-diethylaminoacet-(1-^{14}C)-2',6'-xylidide was obtained from the latter by refluxing it with diethylamine in benzene. In the process of purification the basic properties of the product were utilized.

Thin-layer chromatographic analysis showed that the Lidocaine was radiochemically pure (Fig. 2) .

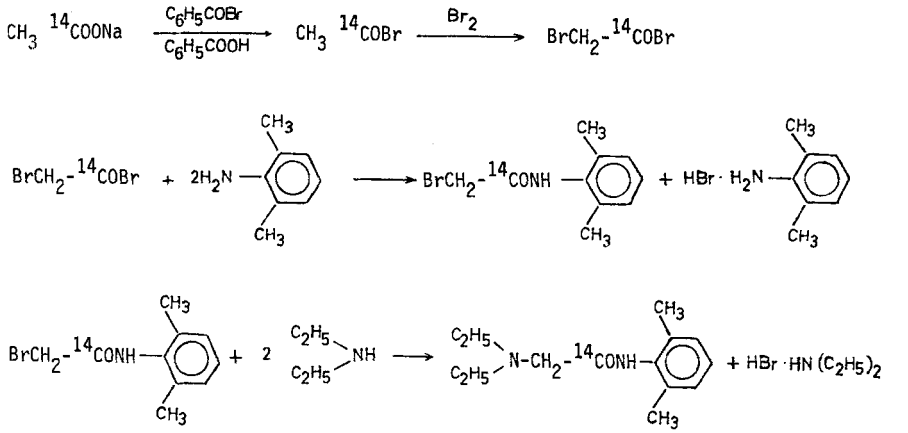

Figure 1.

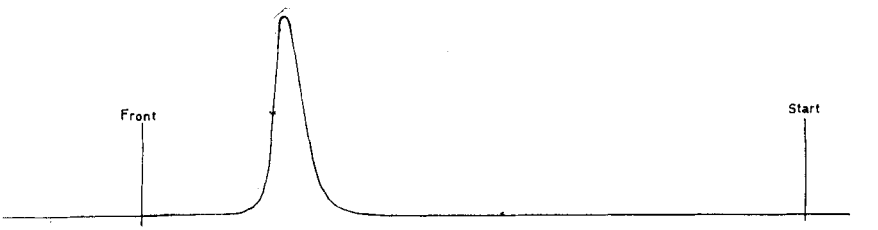

Figure 2.- Radiochromatogram of Lidocaine-^{14}C

EXPERIMENTAL

α-Bromoacet-(1-^{14}C)-2',6'-xylidide.

0.5571 g of sodium acetate-1-^{14}C (specific activity 0.2718 mCi/mg ; total activity 141.45 mCi) was mixed in a Claisen flask with 2.5 g of benzoic acid. Upon the addition of 8 ml of benzoyl bromide, the mixture was slowly distilled over a water bath at about 180°C. The distillation was twice repeated, adding both times 1.5 ml of distilled acetyl bromide to the residue in the flask. The total amount of acetyl-1-^{14}C bromide was 2.7 g (22 mmole).

Next, 1.3 ml 3.9 g (24.4 mmole) of bromine was added dropwise to the acetyl bromide and the mixture left to stand for half an hour at room temperature before completing the reaction at 100 °C for 2 hours. After cooling the resulting mixture to room temperature, the HBr was pumped off for 10 minutes at a pressure of 25 mm Hg. The 3.732 g (18.5 mmole) of red bromoacetyl-1-^{14}C bromide was dissolved in 15 ml of benzene and introduced into a three-necked flask cooled with iced water. A solution of 4.50 g (37.0 mmole) of m-xylidine in 15 ml of benzene was added; the mixture was stirred for 2 hours, filtered and washed with benzene. After drying, the crystalline product was suspended in water, filtered, washed with water, then dried in vacuum over phosphorous pentoxide. A yield of 3.342 g (13.8 mmole) of colourless crystalline α-bromoacet-(1-^{14}C)-2',6'-xylidide was obtained. Specific activity 14.09 μCi/mg; molar activity 3.4 mCi/mmole; recovered activity 47.0 mCi; activity yield 31.0%.

α-Diethylaminoacet-(1-^{14}C)-2',6'-xylidide.

3.340 g (13.8 mmole) of α-bromoacet-(1-^{14}C)-2',6'-xylidide (specific activity 14.09 μCi/mg; total activity 47.0 mCi) was suspended in 40 ml of abs. benzene in a three-necked flask equipped with a stirrer, a cooler and a dropping funnel. 4 ml 2.8 g (38.8 mmole) of diethylamine solution in 20 ml of benzene was added to the suspension. After refluxing for 2 hours, the mixture was cooled to room temperature, the crystallized salt was filtered off and washed with benzene. The benzene filtrate was extracted with 2 N sulfuric acid and the acidic aqueous solution was extracted with benzene. The aqueous extract was made alkaline with concentrated potassium hydroxide solution and the slightly sticky product was filtered off and washed with water. The filtrate was dissolved in acetone, the small amount of insoluble

material filtered off and the residue redissolved in 2 N hydrochloric acid solution . The pale yellow solution was then treated with charcoal; concentrated potassium hydroxide solution was cautiously added to the filtrate . The crystalline product was filtered off, washed with water and dried under vacuum. A yield of 2.5795 g of colourless α-diethylaminoacet-(1-^{14}C)-2',6'-xylidide was obtained; b.p. 63-64°C; specific activity 14.96 μCi/mg; molar activity 3.5 mCi/mmole; recovered activity 38.5 mCi; activity yield 81.5%.

α-Diethylaminoacet-(1-^{14}C)-2',6'-xylidide hydrochloride (Lidocaine hydrochloride).

2.234 g (9.55 mmole) of α-diethylaminoacet-(1-^{14}C)-2',6'-xylidide was dissolved in 10 ml of methanol and 11.0 ml of 1 N methanolic hydrochloric acid. The methanol was distilled off in vacuum. The thick, partly oily, partly crystalline residue was dissolved in 15 ml of abs. ethanol, then filtered, and 90 ml of abs. ether was added to the filtrate. The hydrochloride crystallized out upon scratching. The crystalline suspension was left to stand overnight in the refrigerator. The next day it was filtered off, washed with ether and dried under vacuum. A 1.917 g (yield 74.3%) of colourless, cristalline α-diethylaminoacet-(1-^{14}C)-2',6'-xylidide hydrochloride was obtained. Specific activity 12.87 μCi/mg; molar activity 3.48 mCi/mmole.

The chemical and radiochemical purity of the product was checked by thin-layer chromatography. On a Silicagel "G" layer prepared with 0.1 N sodium hydroxide solution, using as eluent abs. ethanol (25°C), the R_F was 0.79, the purity higher than 99.5%. On the same layer, using an elution mixture of 75-15-10 cyclohexane-benzene-dicyclohexylamine (25°C), the R_F was 0.39, the purity higher than 98%.

The specific activity of the products was measured in a gas ionization chamber with a Nuclear Chicago Dynacon type-6000 vibrating reed electrometer. The activity of the chromatograms was scanned with a Berthold LB-2721-type chromatogram scanner and measured by Berthold LB-2031-type ratemeter.

ACKNOWLEDGMENTS.

We are indebted to Dr. T. Szarvas and Mr. G. Szabó for carrying out the activity measurements and to Mr. L. Baranyai and Mr. F. Horváth for their technical assistance.

REFERENCES.

1. GHANEM, N.A.
Proc. Intern. Conf. Peaceful Uses At. Energy, 3rd, Geneva, 1964, 15, 452.

2. GOSZTONYI, T., WELDE, N.
J. Labelled Compds, 2, 155 (1966).

3. MESHI, T., SATO, Y.
Radioisotopes (Tokyo), 16, 251 (1967).

4. LOFGREN, N.M., LUNDQUIST, B.J.
U.S.Pat. 2, 441, 488;
Swed.Pat. 128, 901.

5. ANKER, H.S.
J. Biol. Chem. 176, 1333 (1948).

6. ROPP, G.A.
J. Am. Chem. Soc. 72, 4459 (1950).